Topical Phenytoin Sodium Dressing In Diabetic Foot Ulcer- A Comparative Study with Povidone Iodine Dressing: A One Year Randomized Controlled Trial

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ACCEPTANCE LETTER

The softcopy of thesis entitled: **"TOPICAL PHENYTOIN SODIUM DRESSING IN DIABETIC FOOT ULCER- A COMPARATIVE STUDY WITH POVIDONE IODINE DRESSING: A ONE YEAR RANDOMIZED CONTROLLED TRIAL"** has been submitted for Anti-Plagiarism check through Turnitin software. The scan has been carried out and the scanned output reveals a match percentage of **03%** which is within the acceptable limits of **10%** as per the guidelines given by UGC.

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LIST OF ABBEVIATIONS USED

CVS	-	Cardio vascular system
DF	-	Diabetic foot
DFU	-	Diabetic foot ulcer
DM	-	Diabetes mellitus
FGF	-	Fibroblast growth factor
GIT	-	Gastro intestinal tract
IDF	-	International Diabetic Federation
IL-1	-	Interleukin-1
PAD	-	Peripheral artery disease
PDGF	-	Platelet derived growth factor
PVD	-	Peripheral vasculardisease
TGF-α	-	Transforming growth factor alfa
TGF-β	-	Transforming growth factor beta
VEGF	-	Vascular endothelial growth factor

ABSTRACT

Background andObjectives

Diabetes is one of the fastest growing global health emergencies of the 21st century.Many complications occur due to hyperglycemia. In a patient with diabetes complications like neuropathy and PAD will lead to foot ulceration.Diabetic foot ulcer contributes for about two thirds of all non-traumatic amputation. Debridement along with regular dressings plays a crucial role in wound healing in diabetics.Phenytoin is used for the treatment of epilepsy and has wound healing properties.It is easy to use, cheap and acquirable easily for medical practice.

Methodology

The present one year randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from January 2019 to December 2019.Thepresent study was comprised of 64 patientssuffering from diabetic foot ulcers divided into two groups of 32 each. For Group A Phenytoin dressing was done and for Group B Povidone iodine dressing was done.

Results

In our study the mean final ulcer area (D14) in group A was 28.77, it was 32.24 in group B, and the difference in area D14 between two groups was statistically significant. (P value 0.0001). Mean final ulcer area between two groups was statistically significant. The mean percentage reduction in area in group A was 19.02 ± 7.27; it was 11.90 ± 3.85 in group B. The difference in percentage reduction in area between two groups was statistically significant. (P value <0.001). These findings suggest that dressing with topical application of phenytoin favours ulcer healing

compared to dressing with povidone iodine.Most of our study results were consistent with previous studies, so age group, sex, socioeconomic status, site of ulcer, onset of ulcer, neuropathy and hypertension can be considered as risk factors for development of foot ulcers in people with diabetes. ‘P’ value for the above mentioned factors was less than 0.05, ruling out bias in our study outcome.

Conclusion and interpretation

In our present study we conclude that use of topical phenytoin dressing for patients with diabetic foot ulcers had beneficial results in progress of ulcer healing in the terms of reduction in area of the wound and compliance of the patients was better with topical phenytoin dressing compared withpovidone iodine dressing. Thus, topical phenytoin wound dressing can be considered as a superior option in the management of diabetic ulcers. But further studies with larger population are required to confirm these observations.

Keywords

Diabetes, Diabetic foot ulcer, Phenytoin, Povidone iodine, Dressing.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Diabetes mellitus (DM) is a chronic, non communicable metabolic disorder leading to high blood sugar levelsdue to the defects in secretion of insulin, action of insulin or both. According to the statistics provided by IDF, at present every 7 seconds a patient suffering from diabetes is likely to die from DM or due to complications of it. Around fifty percent of mortality occurs in the population who are under the age of 60 years.The prevalence may further increase to 9.9% by the year 2045.Fifty percent of the population in developing countries with diabetes are not diagnosed.[1, 2]

DM complications occur among people suffering from diabetes leading to substantial mortality and morbidity. People with diabetes may suffer from microvascular and macrovascular complications.Atherosclerotic changes which lead to cardiovascular disease, stroke, and peripheral artery disease (PAD) are included under macrovascular complications. Nephropathy, neuropathy and retinopathy are included under microvascular complications.[3]

Diabetic foot (DF) is defined as “In a patient with diabetes a foot affected by ulceration, infection and/or destruction of the deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb”. The lifetime risk of patients with diabetesto develop an ulcer is approximately 4–10% it could be up to 25%.15% of population with diabetes are prone to experience diabetic foot ulcer.The amputation risk is 10–15 times more in diabetics than in nondiabetic patients.[4]An ulcer will lead to lower limb amputation in 85% of cases. Amputation is the most dreadful consequence of diabetic foot. After

theamputation diabetic patients are prone to infection, ulceration, may undergo repeat amputation and have high chances of mortality on follow up.[5]

Neuropathy and PAD develop in patients with uncontrolled diabetes by complicated metabolic pathways. Loss of sensation due to neuropathy and ischemia that occurs due to PAD will cause foot ulcers.[6]

In India practices like walking on barefoot, lack of awareness,poor hygiene, hot & humid climatic conditionsleading to profuse sweating, protein deficient diet, poverty and lack of basic medical facilities have aggravated the problem of diabetic foot. Currently topical molecular factors like epidermal growth factors, tissue stimulating factor, vacuum assisted dressing, dressing with hyperbaric oxygen, hydrocolloid wound gels and other wound therapies are being used for wound healing. The cost associated with these therapies is very high and effectiveness of some of the agents is not scientifically demonstrated.[7,8]Iodine based, povidone iodine solution is most commonly used antiseptic solution for diabetic foot dressing. It has good antimicrobicidal properties and has been in usage for antisepsis since years. The disadvantages of povidone iodine are its cytotoxicity to human cells, risk of systemic absorption and delayed wound healing.[12]

Phenytoin (diphenylhydantoin) was first used clinically for treating epilepsy in 1938. Gingival hyperplasia was reported as a side effect to occur in fifty percent of people with epilepsy who were taking oral phenytoin medication for longer time.[9]Phenytoin favors wound healing by increase in the proliferation of fibroblasts, decreasing collagenase activity which promotes collagen formation, hindrance of glucocorticoid activity, decreased exudate formation, enhanced granulation tissue formation, neovascularization and decreases bacterial contamination.[7,8]Phenytoin is

shown to have antibacterial action on Staphylococcus aureus, Escherichia coli, Pseudomonas, Klebsiella species.[10]Phenytoin use has showed good results in the treatment of diabetic ulcers, pressure sores, ulcers due to venous stasis,leprosy, wounds due to trauma and burns.[11]

OBJECTIVES

The objective of this study is to compare the effect of topical phenytoin dressing with povidone iodine dressing for wound size reduction in diabetic foot ulcer.

REVIEW OF LITERATURE

DIABETES MELLITUS-

Definition- According to American Diabetic Association "Diabetes is a group of metabolic diseases which results in hyperglycemia due to the defects in secretion of insulin, action of insulin or both."[13]

DM is mainly characterised by hyperglycaemia. Symptoms of marked hyperglycemia include increased thirst (polydipsia), frequent micturation (polyuria), loss of weight, sometimes associated with blurring of vision and increased hunger (polyphagia). Chronic hyperglycemia may also lead to growth impairment and vulnerable to infections like tuberculosis. Acute conditions of uncontrolled DM are diabetic ketoacidosis or non ketotic hyperosmolar syndrome which may threaten the life. Patients with DM have risk of microvascular damage such as diabetic retinopathy which may lead to loss of sight, nephropathy which may lead to failure of the kidneys and neuropathy which may lead to foot ulcers, charcot joints and amputations. It may also cause autonomic neuropathy causing urogenital symptoms, CVS symptoms, GIT symptoms and sexual dysfunction. People with DM are more prone to macrovascular complications like ischemic heart disease, stroke, PVD , hypertension and lipoprotein metabolism abnormalities.[2,3,13] In diabetics beta cells of pancreas are destroyed which will lead to deficiency of insulin and some develop resistance to action of insulin by several mechanisms leading to it. Carbohydrate, protein and fat metabolism abnormalities occur from lack of insulin leading to inadequate action of insulin on target tissues.[14]

EPIDEOMOLOGY-

According to International Diabetes Federation (IDF)[15]in 2019 approximately

• "463 million adults aged between 20-79 years were living with diabetes; by the year 2045 this number may rise to 700 million.

• The percentage of people with type 2 diabetes is increasing in most countries.

• 79% of adults suffering with diabetes were living in middle and low income countries.

• One in five of the people who are aged above 65 years old has diabetes.

• Deaths caused by diabetes were 4.2 million.

• 374 million people are at high risk of developing type 2 diabetes."

India has the second largest number (77 million) of adult population with diabetes worldwide. India is considered as one of the epicentres of the worlds DM pandemic. Indian population are at increased risk of developing DM due to a particular phenotype, shown as resistance to insulin despite of having low body mass index and elevated levels of intra abdominal fat along with demographic changes which were rapid. The prevalence of DM has risen in both rural and urban parts of the India involving population of all socioeconomic status since the 1960's.[16]

Classification-[17, 18]

1. Type one diabetes- In this type destruction of beta cells of pancreas occurs due to autoimmune cause and leads to an absolute insulin deficiency. It is also called as Latent Autoimmune Diabetes in Adults, accounting for only 5–10% of patients with diabetes.

2. Type two diabetes- In this type decreased secretion of insulin occurs from the beta cells of pancreas and resistance to insulin develops. It is often associated with other

disorders (e. g. metabolic syndrome). It accounts for 90–95% of patients with diabetes.

3. Gestational diabetes- It is diagnosed in the 2nd or 3rd trimester of pregnancy with no prior history of DM.

4. Other types-

• Diseases of exocrine pancreas such as cystic fibrosis, pancreatitis, hemochromatosis.

• Endocrinopathies such as acromegaly, cushing syndrome, pheochromocytoma.

• Drug or chemically induced (e. g. glucocorticoids, neuroleptics, beta blockers, calcium channel blockers, during the treatment of HIV/AIDS, or after organ transplantation).

• Genetic defects of the beta cell function like Maturity onset diabetes of the young.

• Infections

Diagnostic criteria for DM-[18]

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

Figure 1- Diagnostic criteria for DM

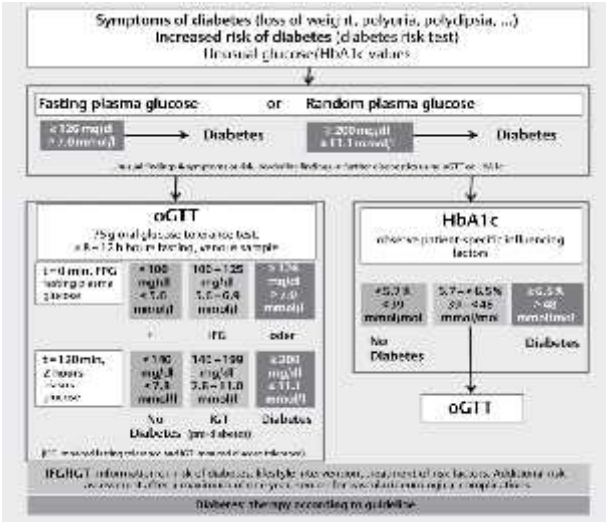


Figure 2 – Diagnostic approach for diagnosing DM

Diabetic Foot-

Definition- "In a patient with diabetes a foot affected by ulceration, infection and/or destruction of the deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb".[19]

Epidemiology-

In a person with diabetes chances of developing a foot ulcer in his lifetime is as high as 25%. Studies report that diabetic foot ulcerations will lead to 85% of lower limb amputations.It is reported that around 40-70% of all the amputations of lower limbs excluding trauma are done in people suffering with DM. Diabetic foot ulcer is the leading reason for hospital admission in patients suffering from diabetes.[19,20]

Anatomy of Foot-[21, 22]

The foot is located distal to the ankle that bears the body when standing and provides support to walk and run. Foot adapts its shape to uneven surfaces due to its construction in the form of arches. The framework of the foot is made of 7 tarsal bones, 5 metatarsals, and 14 phalanges. The foot is divided into 3 functional and anatomical zones. Talus and calcaneus will form hind foot. Navicular, cuboid and cuneiform will form mid foot. Metatarsals and phalanges will form forefoot.

In anatomical terms, the foot is called pes. The top of the foot is known as dorsum of the foot which is directed superiorly. The bottom of foot is known as the sole or plantar side or ventral side or inferior aspect. The heel region is formed by sole of the foot which underlies the calcaneus, and ball of foot is formed by sole which underlies the medial 2 metatarsal heads. The great toe (big toe) is digit 1 or the hallux. The little toe is also the 5^{th} toe.

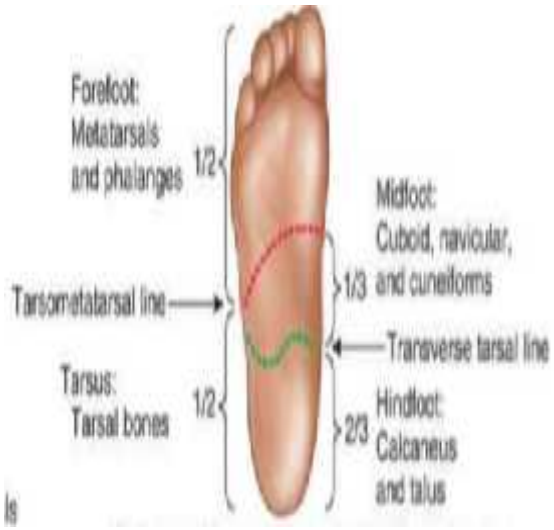


Figure 3- Anatomy of foot

SKIN AND SUBCUTANEOUS TISSUE-[21, 22]

Skin over the foot has varying degrees of thickness and texture. The skin over the dorsum of foot is thin and less sensitive. Subcutaneous tissue over the dorsal surface is loose which will make the oedema more prominent, especially around the medial malleolus and anterior to it. The heel, ball of the foot and lateral margin of the foot are vital weight bearing areas of foot, having thick skin in these areas. The subcutaneous tissue in the plantar aspect of foot is more fibrous compared to dorsal aspect of the foot.

Skin ligaments called as fibrous septa divides the subcutaneous tissue in to small fat filled areas, which acts as a shock absorber especially over heel area. Sweat glands are present in large numbers over the sole which keeps the skin moist and prevents ulceration, but hair follicles are absent over the sole.

DEEP FASCIA OF FOOT-

It is thin and is connected with inferior extensor retinaculum proximally and connected with plantar fascia on the lateral and posterior aspect. Parts of the foot are

held together by plantar fascia and protect the underlying nerves, blood vessels, muscles from injury. It also supports the longitudinal arches of the foot.

MUSCLES OF FOOT-[21, 22, 23]

Foot consists of 20 individual muscles, of which 14 muscles are situated on plantar aspect, 2 muscles are situated on dorsal aspect, and 4 muscles are situated intermediately.

Dorsal aspect-

Extensor DigitorumBrevis

Extensor HallucisBrevis

Ventral aspect-

Layer	Muscles	Features
First layer	1. Flexor digitorum brevis. 2. Abductor hallucis. 3. Abductor digiti minimi	They cover whole of the sole
Second layer	1.Flexor digitorum accessories 2.Four lumbricals. 3.Two tendons (tendon of flexor digitorum longus and tendon of flexor hallucis longus)	Flexor digitorum accessorius and lumbricals are attached to the tendon of flexor digitorum longus
Third layer	1. Flexor hallucis brevis. 2. Flexor digiti minimi brevis. 3. Adductor hallucis	1. They are confined to the metatarsal region of the sole. 2. Two of these muscles act on the big toe and one on the little toe
Fourth layer	1. Interossei (3 plantar interossei and 4 dorsal interossei). 2. Tendon of tibialis posterior. 3. Tendon of peroneus longus	They fill up the intermetatarsal spaces

Table no1- Muscles of Ventral aspect of foot

The main function of the muscles of the foot is to support the arches of foot.

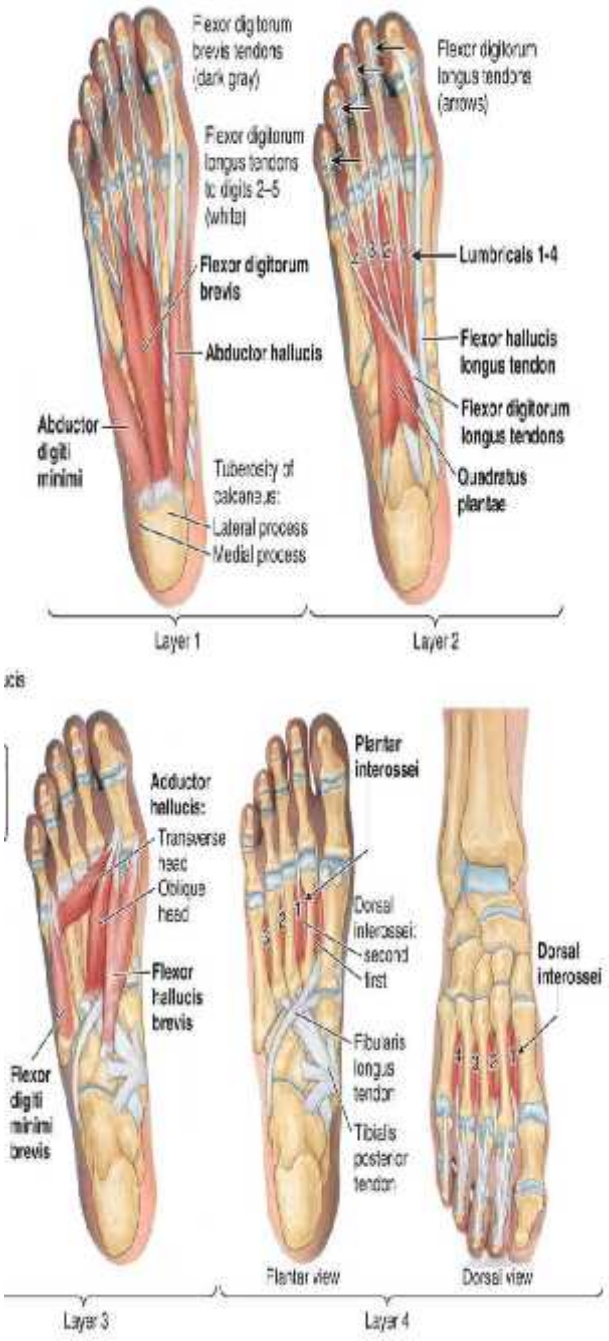


Figure 4- Muscles of foot

Arterial Supply of foot-[21, 22]

Dorsum of the foot-

Dorsalispedis artery- Anterior tibial artery continues as dorsalispedis artery and supplies the dorsum of foot.

BRANCHES-

1. Lateral tarsal artery

2. Arcuate artery

3. 1st dorsal metatarsal artery

4. Deep plantar artery

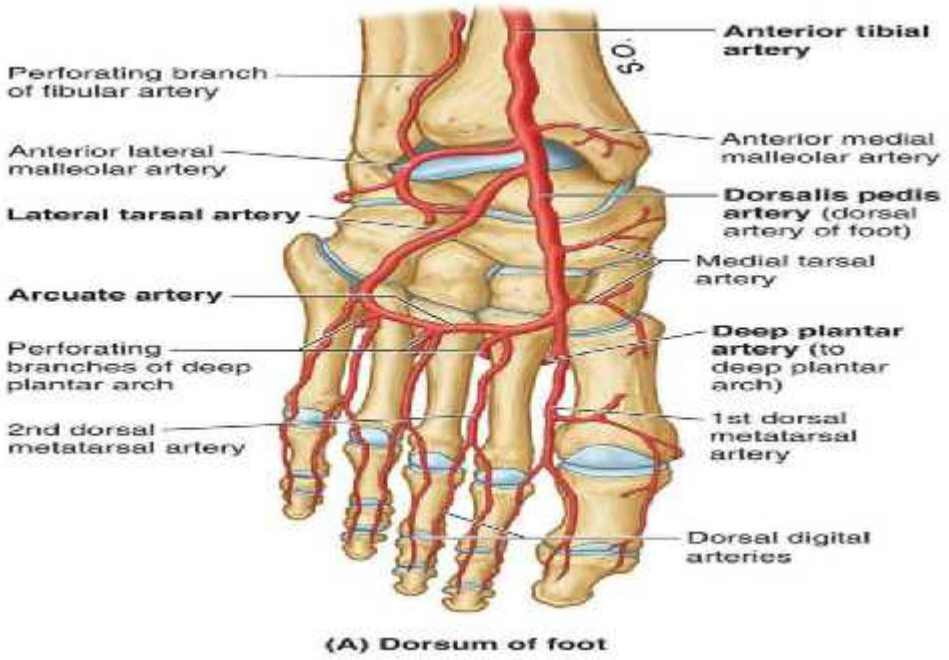


Figure 5- Arterial supply of Dorsum foot

Sole of the foot-

Posterior tibial artery- It runs in the rear of medial malleolus, located under the flexor retinaculum.

Branches-

1. Medial Plantar Artery

2. Lateral Plantar Artery

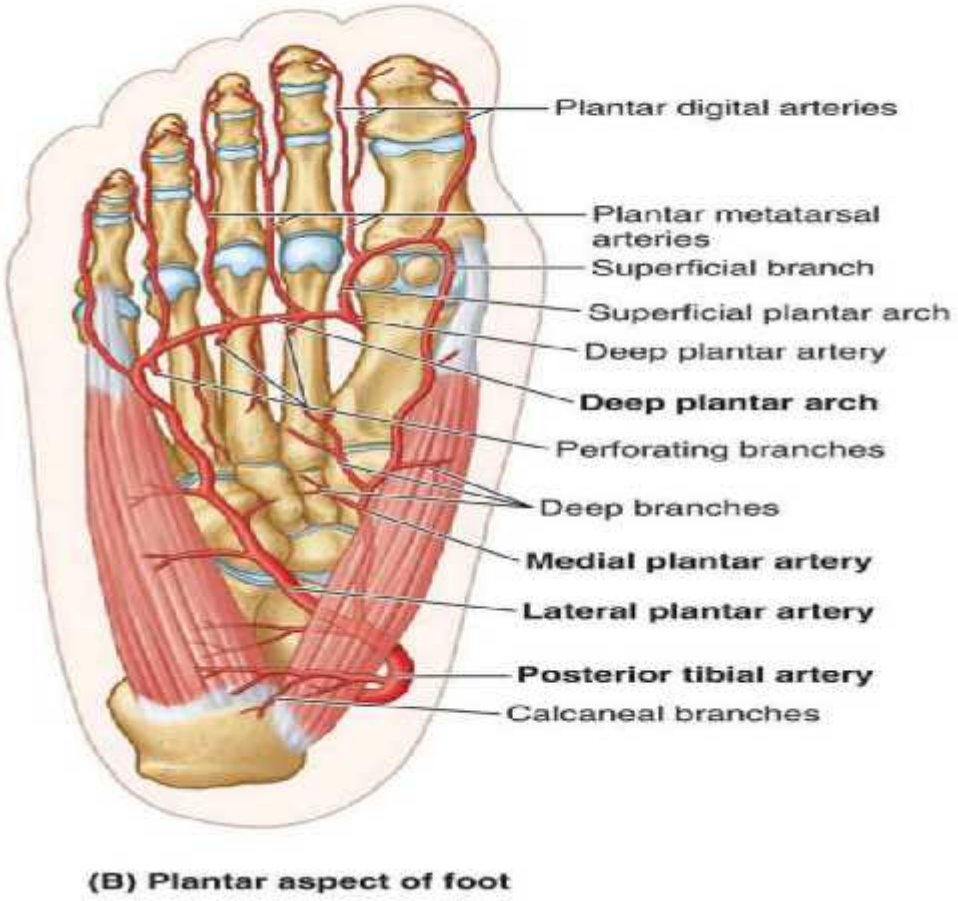


Figure 6- Arterial supply of plantar aspect of foot

NERVE SUPPLY-[21, 22]

Dorsum of foot-

1. Superficial peroneal nerve

2. Deep fibular (peroneal) nerve

3. Saphenous nerve

4. Sural nerve

5. Medial and lateral plantar nerves

Sole of foot-

Tibial nerve- It passes behind the medial malleolus, deep to the flexor retinaculum and divides into

1. Medial Plantar Nerve

2. Lateral Plantar Nerve

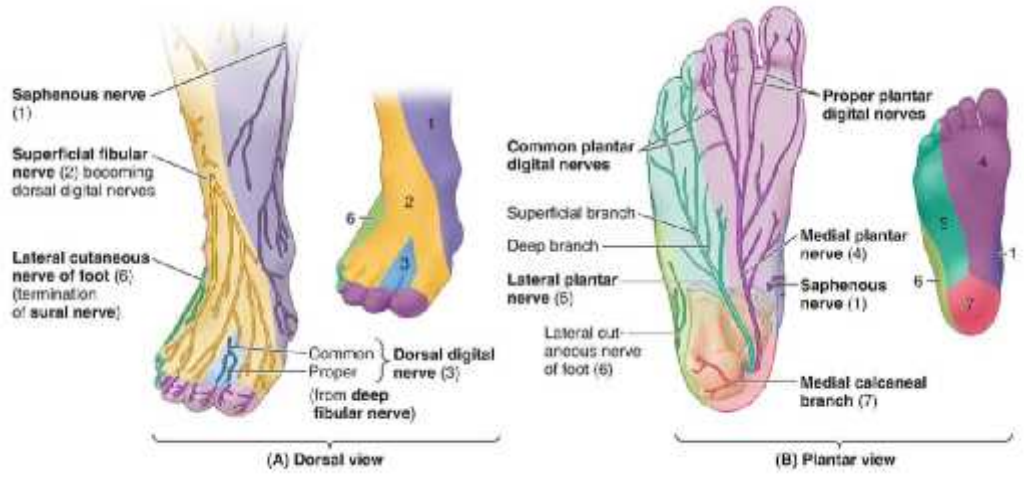


Figure 7- Nerve supply of foot

ARCHES OF THE FOOT-[21, 23] Three main arches are present in the foot

1. Medial longitudinal arch

2. Lateral longitudinal arch

3. Transverse arch

Functions-

1. Weight over the foot is distributed by them and acts as shock absorbers during walking, jumping and running.

2. They help in adaptation of foot to changes in surface contour.

3. They distribute body weight to the weight bearing areas of sole mainly to heel and the base of the toes.

Peripheral neuropathy in diabetics is the main factor that causes the arches of foot to collapse which causes increased trauma to soft tissue.

WOUND HEALING-[24, 25, 26]

The process of wound healing can be divided into 4 parts: haemostasis, inflammation, proliferation and maturation or remodelling. All these parts are overlapping in the process of wound healing.

1. Haemostasis-

Immediate response of the body after injury is to start coagulation and achieve haemostasis in the wound. This occurs to prevent exsanguinations. Smooth muscle located in the wall of damaged arteries contract as they constrict, which occurs due to increased levels of calcium in the cytoplasm. This contraction can seal the vessels as small as 5mm.

The arterial contraction will last for only few minutes until hypoxia and acidosis in the wound wall occurs, which leads to reflux vasodilatation there by relaxing the arteries due to the production of nitric oxide and adenosine. Release of histamine from mast cells increases the vascular permeability and entry of inflammatory cells into the extracellular space around the wound which explains the characteristic warm, red, swollen features of acute wounds.

Further bleeding is prevented by the coagulation cascade which is triggered by extrinsic and intrinsic pathways forming aggregation of platelets and clot formation. Platelets, excluding the role in clot formation also release multiple growth factors and cytokines which play important role in the healing cascade. These importantly include platelet derived growth factor (PDGF), fibroblast growth factor (FGF) and transforming growth factor (TGF) β. They also help in attracting and activating neutrophils, endothelial cells, macrophages, fibroblasts and promote wound healing.

2. INFLAMMATORY PHASE-

The main role of inflammatory phase is to establish a barrier against invading micro-organisms, to prevent infection as the mechanical barrier is damaged. It is divided in to early and late inflammatory phase.

a. Early inflammatory phase-

It initiates molecular events by activating complement cascade which leads to neutrophilic infiltration of the wound site and prevent infection. The neutrophils are the first responders and appear at the wound site by 24 – 36 h after injury, mediated by multiple chemo attractive agents like transforming growth factor beta and complement components. Neutrophils destroy and clear foreign particles, damaged tissue and bacteria by

1. Phagocytosis

2. Neutrophils degranulate and release substances like proteases, lactoferrin and neutrophil elastase. They are toxic and will and destroy bacteria and dead tissue.

3. Protease and chromatin traps produced by them helps to catch and destroy bacteria. Neutrophil activity will produce oxygen free radicals; they help in destroying the bacteria. After completing the task neutrophils are phagocytised by macrophages or removed by apoptosis.

b. Late inflammatory phase-

The process of phagocytosis is continued by large phagocytic cells called as macrophages after 48 to 72 hrs. Various chemo attractive agents like PDGF, leukotriene B4, elastin, platelet factor IV and TGF-β attract macrophages to the site of injury. They will provide tissue growth factors like TGF-β, TGF-α, epidermal growth factor, fibroblast growth factor [FGF] and collagenase which promote angiogenesis. Lymphocytes will appear at the wound site after 72 hrs which are attracted by the

interleukin-1 (IL-1), immunoglobulin G breakdown products and components of complement pathway. Interleukin-1 helps in collagen remodelling and produces extracellular matrix scaffold.

3. PROLIFERATIVE PHASE-

This phase starts after injuring stimulus has been stopped, after complete haemostasis occurs, after an immune response occurs and wound is free of debris. This phase takes place on the 3rd day after injury occurs and will continue for 2 weeks. This phase includes

Fibroblast migration- After the injury by third day fibroblasts proliferate and factors like TGF-β and PDGF attract them leading to their immigration into the wound. Matrix proteins like hyaluronan, proteoglycans, fibronectin and type one and three procollagen are produced by them by proliferation. The pink, vascular tissue formed is called as granulation tissue which is made of several types of collagens. Now, fibroblasts change to myofibroblasts containing actin bundles and extend pseudopodia actively, allying to collagen and fibronectin in the extracellular matrix. By the retraction of these cell extensions wound contraction takes place which helps in the approximation of the wound edges.

Collagen synthesis- Collagens which are produced by fibroblasts make the tissues durable and add strength to the tissues. They play an important role mainly in proliferative and remodelling phases of wound healing.

Angiogenesis- Formation of the new blood vessels occurs by endothelial cells stimulated by release of PDGF, TGF-alpha, TGF-beta Fibroblast growth factor and vascular endothelial growth factor(VEGF).

Epithelialisation- Epithelialisation starts with in few hours after injury from the edges of wound. Initially one layer of cells are formed over the defect followed by increased mitotic activity of them around edges of the wound.

4. REMODELLING PHASE-

This phase may continue up to two years. It involves maturation of collagen, realignment of collagen fibres, wound contraction and decreases wound vascularity. The tensile strength of the wound is increased it is maximum by the end of 12th week and is around 80 percent of normal skin.

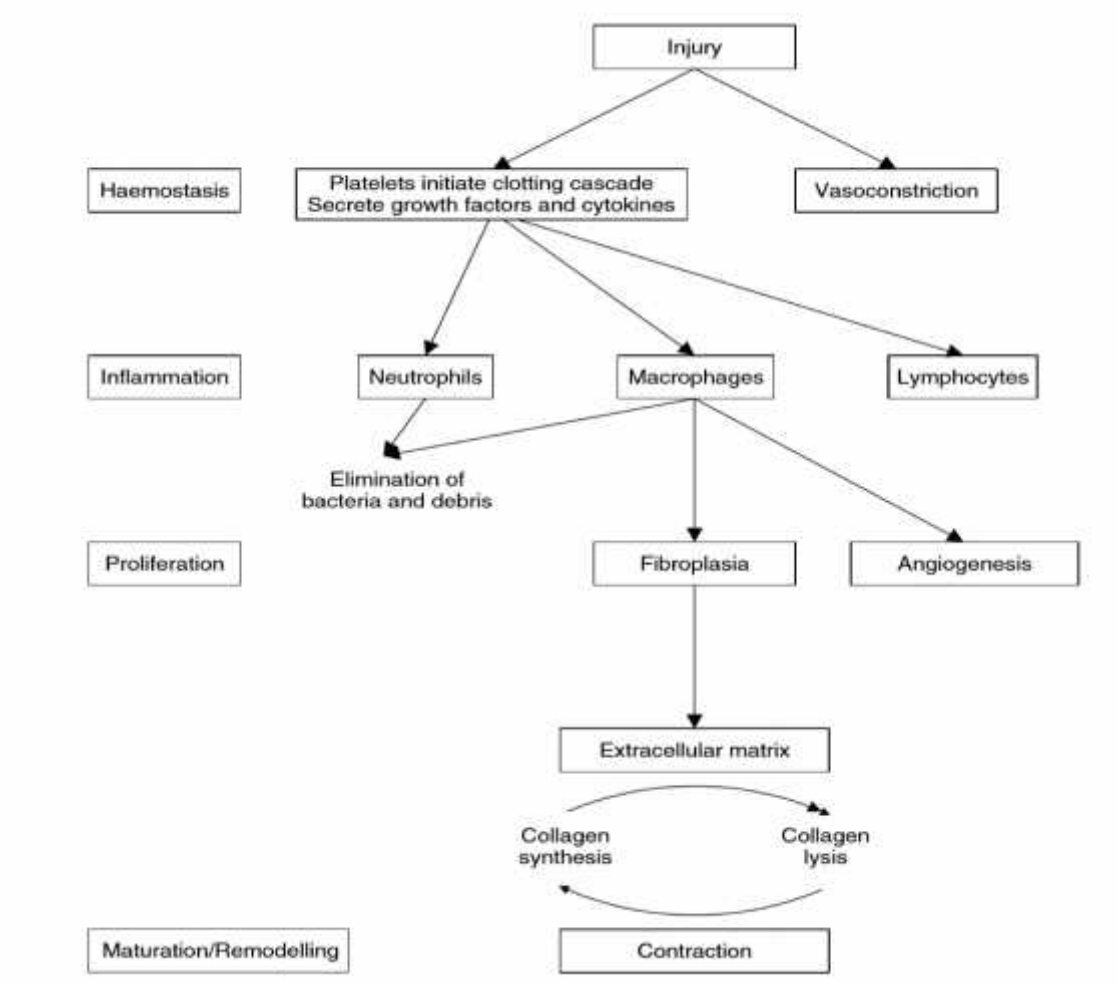


Figure 8- Process of wound healing

Pathogenesis of diabetic foot ulcer-

DFU occurs as a consequence of various contributing factors like neuropathy, ischemia from PVD, deformities of the foot, injuries to the foot and decreased resistance to infections.[27]

1. Neuropathy- 66% of people will develop DFU as a consequence of neuropathy. Neuropathy leads to impairment of movements and sensation, severity depends upon the nerve affected. Various studies state that abnormalities in the metabolism due to hyperglycemia will cause neuropathy. Nerve damage due to hyperglycemia occurs as a result of polyol pathway, elevated levels of intracellular advanced glycated end products, and increased hexosamine pathway flux.[27] Neuropathy in diabetics occurs in the motor, sensory and autonomic nervous systems.[28] Motor neuropathy will cause foot deformities like hammered toes, charcot foot or restriction of joint motility leading to abnormal pressure over foot leading to the formation of callus. Due to undetected repetitive injury over the callus, inflammation and tissue death occurs leading to ulceration.[29] Sensory neuropathy leads to damage of sensory nerves leading to loss sensation of pain and due to loss of this protective sensation ulcers are formed from repetitive trauma, exposure to heat and ill fitting foot wear. Autonomic neuropathy will affect the functioning capacity of sweat glands. The skin becomes dry as moisturizing ability is lost leading to cracks and development of infection.[27, 28, 29]

2. Peripheral vascular disease- Peripheral vascular disease will cause 50% of diabetic foot ulcers. Diabetic patients have a high risk of atherosclerosis, endothelial proliferation, thickening of basement membranes of capillaries and hardening of arteriolar walls. It affects the tibial and peroneal arteries of the calf most often. Hyperglycemia is associated with elevated levels of thromboxane A^2 which leads to platelet aggregation and vasoconstriction, thus increasing the risk of plasma

hypercoagulability in diabetics. Diabetes is commonly associated with smoking, hyperlipidemia and hypertension, also contribute to PVD. Diabetics have decreased arterial blood supply leading to peripheral ischemia and ulceration.[27, 28]

3. Infections- As an ulcer develops, barrier function is lost and susceptibility to infection occurs. In chronic ulcers, a biofilm is formed by microorganisms due to their aggregation. This biofilm increases resistance to antimicrobials and chemical attacks, leading to delayed wound healing. Leukocyte function is also affected in diabetics causing decreased host resistance and increased susceptibility for superficial and deep infections.[29]

4. Delayed Wound Healing- It occurs due to neuropathy and PVD. Both excessive and inadequate angiogenesis with defective macrophage function is seen in diabetics leading to delayed wound healing.[5]

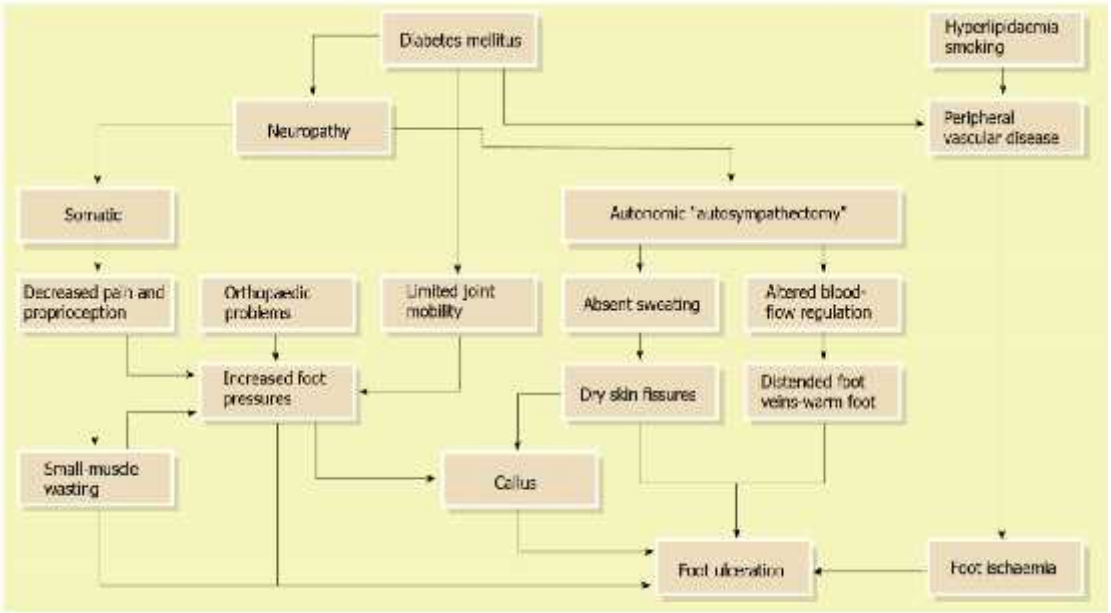


Figure 9- Pathology of Diabetic foot ulcer

CLINICAL EXAMINATION OF DIABETIC FOOT

Diabetic ulcer- Factors that produce diabetic ulcer are (i) Diabetic neuropathy (ii) Diabetic atherosclerosis which leads to ischemia (iii) Glucose rich tissue is more prone to infection which leads to infection. Trophic ulcers are caused due to neuropathy. Arterial ulcers are caused due to ischemia.

A patient with diabetes may have-

1. Dry skin- Autonomic neuropathy will affect the functioning capacity of sweat glands. The skin becomes dry as moisturizing ability is lost leading to cracks and development of infection.
2. Calluses- A callus is a growth of hard skin on the underside of the foot. They are caused by an uneven distribution of weight and by ill fitting shoes.
3. Corns- A corn is a growth of hard skin near a bony area of a toe or between toes. They occur due to pressure from shoes over the toes or by friction between the toes.
4. Blisters- They occur over the foot of patients and may lead to infection.
5. Bunion- Bunion occurs when the great toe bends towards the second toe. It may cause pain and deformity.
6. Hammertoe- It occurs due to a weakened muscle which makes the tendons of the toe shorter, causing the toe to curl under the foot. They may cause difficulty in walking, blisters and calluses.
7. Plantar warts- They occur over the heel or ball of the foot and have tiny black spot in the centre. They cause pain.
8. Ingrown toe nails- They occur when edges of nail grows in to the skin, occur due to pressure from the shoe. They are painful and may cause infection, swelling, redness and abscess.
9. Athlete's foot- It is caused by fungus leading to itching and cracking.

10. Charcot foot- It affects the joints, bones and soft tissues of foot and ankle leading to deformity, destruction and dislocation. It occurs due to neuropathy.
11. Abscess- Infections may lead to formation of pus known as abscess. It requires drainage.
12. Gangrene- Inadequate perfusion leads to tissue necrosis and formation of gangrene.

PALPATION OF ARTERIES-

The dorsalispedis artery is felt just lateral to the tendon of the extensor hallucislongus at proximal end of 1^{st} web space.

The posterior tibial artery is felt against the calcaneus just behind the medial malleolus midway between it and the tendoachilles.

The anterior tibial artery is felt in the midway anteriorly between medial and lateral malleolus against the lower end of tibia just above the ankle joint and just lateral to the tendon of the extensor hallucislongus which is made prominent by asking the patient to extend his great toe.

The popliteal artery is difficult to feel as it lies deep behind the knee. The knee is flexed about 45^{o} with the heel resting on the bed, so that the muscles around the popliteal fossa are relaxed. It is felt in lower part of fossa over flat posterior surface of upper end of tibia.

The femoral artery is felt at the groin just below the inguinal ligament midway between the anterior superior iliac spine and symphysis pubis.

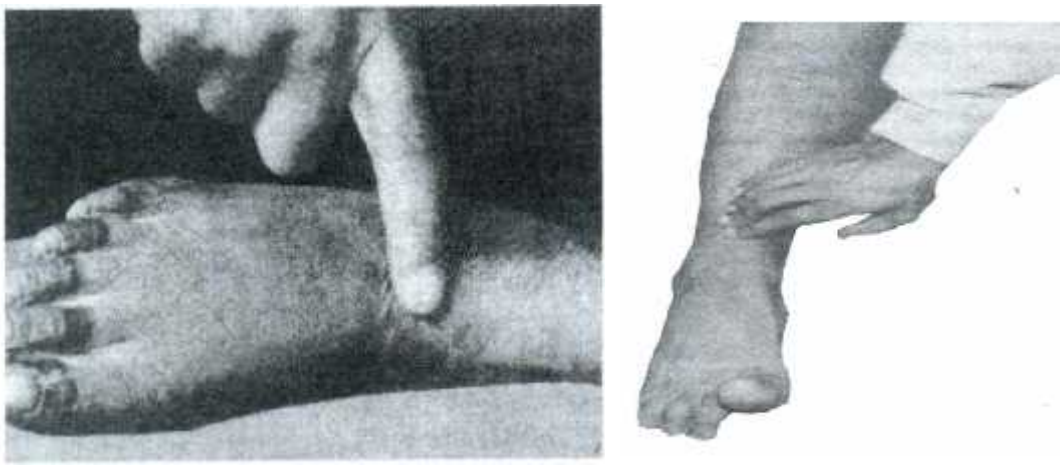


Figure 10- Palpation of Dorsalispedis and Anterior tibial pulsations

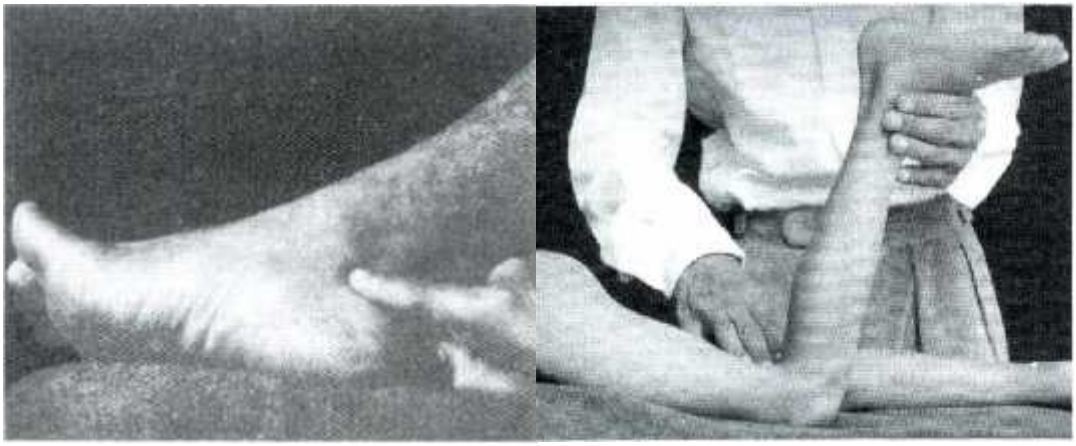


Figure 11- Palpation of Posterior tibial and popliteal pulsations

NEUROLOGIC ASSESSMENT- It is done by

1. Monofilament test.
2. Tuning fork and visual perception tests
3. Pinprick test

VASCULAR ASSESSMENT- It is done by using

1. The ankle brachial index
2. The toe brachial index
3. Doppler Ultrasound

CLASSIFICATION OF DIABETIC FOOT ULCERS-[30]

DFU should be assessed thoroughly and they should be classified properly for the correct care of the diabetic foot, as diabetic ulcer may lead to the amputation in patients with diabetes.

Wagner–Meggit classification system-[27]

It is most widely used classification for DFU. It is composed of 6 grades which includes depth of ulcer, level of tissue necrosis and gangrene. It does not include ischemia, infection and other comorbid factors.

Grade	Foot lesion
0	No open lesions or cellulitis
1	Superficial ulcer
2	Deep ulcer upto tendons and joint tissue
3	Deep ulcer with abscess, osteomyelitis and joint sepsis
4	Local gangrene forefoot or heel
5	Gangrene of entire foot

University Of Texas classification[27]-

It includes depth of the wound, limb ischemia, infection. There are A-D stages and 0-3 grades. Wounds with higher stages or grades require vascular repair or amputation as they as less prone for healing. This system is superior to Wagner–Meggit classification system.

Stages	Grades			
	0	1	2	3
A	Healed pre or post ulcerative lesion completely epithelialized	Superficial wound not involving bone tendon or capsule	Wound penetrating tendon and capsule	Wound penetrating to bone or joint
B	With infection	With infection	With infection	With infection
C	With ischemia	With ischemia	With ischemia	With ischemia
D	With infection and with ischemia	With infection and with ischemia	With infection and with ischemia	With infection and with ischemia

International working group classification-[27]

Risk group 0	No neuropathy, no PVD
Risk Group 1	Neuropathy, no-deformity PVD
Risk Group 2	Neuropathy and deformity and or PVD
Risk Group 3	History pathology

MANAGEMENT-

ASSESSMENT OF ETIOLOGY-

1. Detection of neuropathy- It is diagnosed by physical examination of the feet and history.

a. Symptom scores- They are used to evaluate the symptoms due to neuropathy and response to the treatment. Diabetics with painful neuropathy are evaluated using symptom scores. The Neuropathy Symptom Score (NSS) has high validity and sensitivity and is used commonly.[30]

b. Semmes Weinstein monofilament test- Monofilament test is the cheap and most widely used for examination of foot at risk of neuropathy. The inability to sense or loss of sensation to 10g pressure is defined as loss of pain sensation. This test is easily done and accepted by the patients easily.

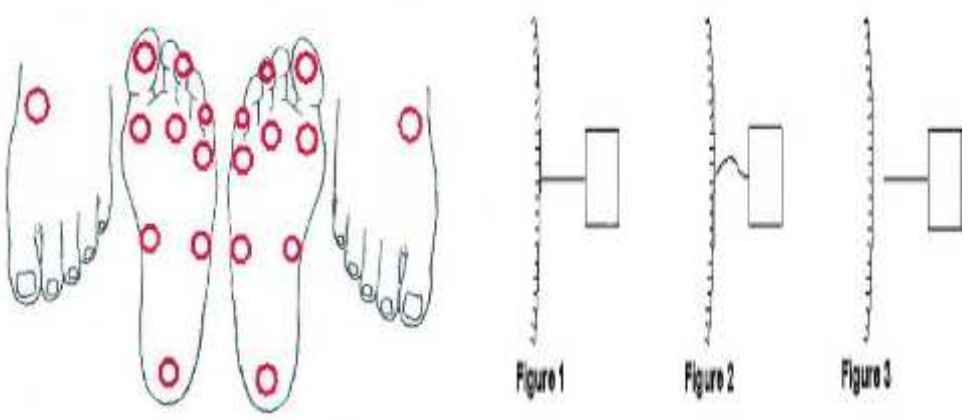


Figure 12-Semmes-Weinstein monofilament test

c.Vibration perception- Loss or deterioration of sense of vibration is the earliest sign of peripheral diabetic neuropathy. It can be tested by 128 Hz tuning fork, graduated rydelseiffer tuning fork, neurothesiometer and biothesiometer.

d. Nerve conduction studies- Diabetics with asymptomatic peripheral neuropathy are evaluated by these studies to know the advancement of the disease. They are not widely used.

e. Nerve biopsy and Skin biopsy are also done rarely for detection of diabetic neuropathy.[30]

2. DIAGNOSIS OF PERIPHERAL ARTERIAL DISEASE-

a. The ankle brachial index- It is the ratio of pressure at the ankle and pressure at the arm, measured using doppler. It is used for detection of PAD. In diabetics calcified, noncompressible arteries may lead to falsely elevated values of ankle-brachial index.

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

b. The toe-brachial index- It is used if ankle brachial index values are more than 1.30 because lower limb has smaller arteries which are not prone for calcification. Values less than 0.70 are suggestive of PAD.

Ultrasound velocity spectroscopy and imaging, Computed tomographic angiography, Contrast angiography are the other methods used for the diagnosis of PAD.[30]

INVESTIGATIONS- The following investigations should be done

1. Complete blood count to see the total leukocyte count and look for any infection.

2. Kidney function tests to rule out diabetic nephropathy.

3. HbA1C is an important indicator of long term glycemic control which reflects the average plasma glucose of the past two to three months. Glycemic control is important for the patient as poor glycemic control leads to poor wound healing.

4. Foot X ray to rule out osteomyelitis, foot deformities.

5. Discharge of Wound for culture and sensitivity.

6. UKB to rule out ketoacidosis.

TREATMENT-

1. Education- Effective education about the foot care in diabetics can prevent around fifty percent of ulcers in diabetics. Diabetic patients should know about the factors causing DFU, significance of foot care which involves self inspection of the foot, hygiene of the foot and use of proper footwear.[31]

2. Blood sugar control- Inadequate control of blood sugar control is considered as the primary cause of diabetic foot ulcer. High blood sugar level decreases host response to an infection by suppressing inflammatory response. Poor glycemic control also accelerates the manifestation of PAD.[31]

3. Debridement- It is the removal of necrotic tissue and debris along with infected materials and foreign bodies from a wound. It is the initial step in the management of the wound and promotes wound closure by growth of the granulation tissue and stimulating growth factors. There are different kinds of debridement including surgical, autolytic, enzymatic, mechanical, and biological.[30, 31]

a. Surgical debridement- It is also called as sharp debridement, done by using a scalpel or curved scissors. Dead, necrotic and infected tissues are removed until base of the ulcer bleeds. Care should be taken to protect granulation tissue. This procedure turns a chronic ulcer in to an acute one.[30, 31]

b. Autolytic debridement- A moist wound environment is created using a dressing and natural host defences clears the dead and necrotic tissue by using bodies enzymes, avoiding damage to healthy tissue. Hydrocolloids and hydrogels are used for promoting autolytic debridemement. It is useful for an extremely painful wound.[19, 31]

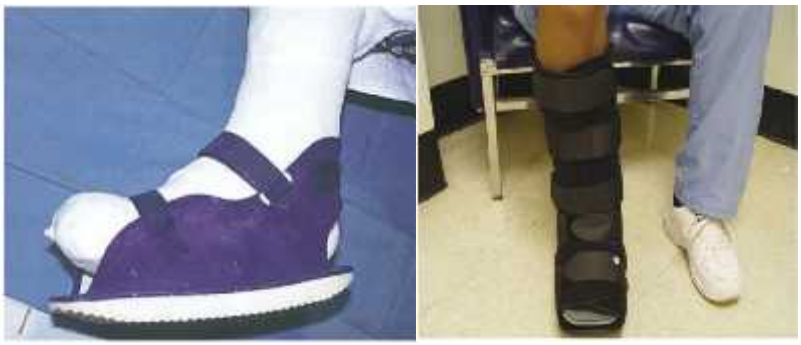
c. Enzymatic debridement- Topical agents are applied on the ulcer once daily. Enzymes like streptokinase, papain, trypsin, papainurea and streptodornase digest and destroy the necrotic tissue. These topical agents are of high cost, long time application is needed and may cause allergic reactions.[30, 31]

d. Mechanical debridement- Wet to dry dressings, hydrotherapy or irrigation with high pressure are used for mechanical debridement. It can remove viable tissues along with dead tissues casuing to pain.[30]

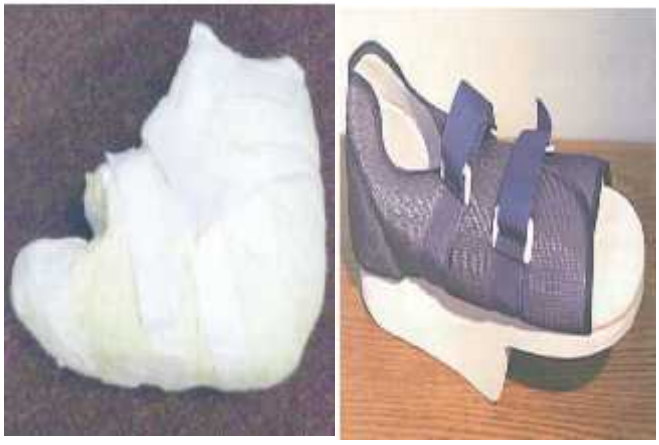
e. Biological debridement- Sterile maggots are placed on the wound directly and held in place with the help of a dressing. These maggots help in the elimination of necrotic tissue and decrease the bacterial load leaving the healthy tissue unaffected. It is expensive and refusal by the patients for the usage of maggots are the disadvantages.[31]

4. Infection Control- Infection control is crucial in diabetic foot patients, as they are at high risk of limb amputation. Treatment should be aggressive because at times it may threaten life. Superficial foot infections are treated by using regular dressings and oral antibiotics. Moderate or deep infections needs admission in hospital and intravenous antibiotics. Antibiotic therapy should be based on the wound culture.

5. Offloading- It is known as pressure modulation and it is important for treating diabetic neuropathic ulcers. Offloading provided properly promotes healing of diabetic ulcer. Several offloading techniques such as total contact casting (TCC), Removable cast walker, half shoes, scotch cast boot and felted foam dressings are available. Total contact casts (TCC) is considered most effective. This cast protects the wound site by relieving the pressure and distributing the pressure over the entire surface of foot. It has several disadvantages such as need of an expert and skill to apply the cast, secondary skin irritation may occur and assessment of the ulcer cannot be done daily. Other devices like half shoe and short leg walker can also be used and are preferred by patients because they are inexpensive and easy to apply. Disadvantage is that they can be removed by patients and patient's compliance cannot be ensured with less significant pressure relieving results.[30, 31]



Total contact cast Removable cast walker



Scotch-cast boot Half shoe

Figure 13- Various types of Offloading devices

Wound care – Dressings-

Wound care is important, part of which involves dressing of the wound. Dressing is meant to be in contact with wound and bandage is that which holds the dressing in place.[32]

HISTORY-[32, 33, 34]

Clay tablets were used for the treatment of wounds from about 2500 BCE. Ancient Egyptians used donkey faeces to pack the wound as open wound was known as a door way for entry of demons, so it was used as a repellent. Though it was unacceptable donkey faeces is considered to have proteins as trypsin and antibiotic properties which helped in wound healing.Fresh meat was used to cover the open wounds followed by treatment with honey or herbs.

Plasters which were considered equivalent to present day dressings were used, made of clay, herbs, oil or grease. They were used to occlude the wounds and absorption of exudates from the wound. Hippocrates proposed the use of vinegar or wine for cleaning the wounds. Grease made from the animal fat and honey were used to apply over the wounds as they have antibacterial activity. Honey is the part of many dressings till now because it is known for its effective antibacterial activity. Wool was boiled in water and used as a bandage.

In 19th century after the advent of need for antisepsis of the wound and infections were controlled by using antibiotics.

In 20th century modern wound healing principles were introduced, not less than 4,000 wound care products are available now. Dressings have been added with the properties like debridement, moisturisation, promotion of growth, antibiotics.

Characteristic features of ideal wound dressing-[32, 35]

1. Should maintain high humidity at the wound site.
2. Should absorb excess exudates.
3. Non-toxic and non-allergenic.
4. Free of toxic wound contaminants and particles.
5. Impermeable to bacteria.
6. Should allow gaseous exchange.
7. Should protect the wound from additional trauma and can be taken out easily.
8. Cost effective and long shelf life.
9. Should require only infrequent changes.

All the characteristic features cannot be present in a single dressing.

Types of dressings-[32, 33, 36]

1. **Wet to dry dressing or simple saline-** They help in preparation of wound bed due to debriding action. It helps in the absorption of exudates. It is cheapest dressings used and requires frequent change.
2. **Antibacterial agents-** Antibiotics like metronidazole, neomycin, gentamycin and mupirocin can be used topically as they have good antibacterial coverage. They can be used alone or in combination with other types of dressings.
3. **Tulle dressings-** Gauze dressings are impregnated with paraffin and used. Dressing becomes less adherant and helps in easy removal avoiding trauma. They are used in superficial clean wounds, skin grafts, granulating and epithelising wounds.
4. **Polyurethane foam-** Theyare nonsticking, allows moisture to escape and absorb lots of discharge.They prevent maceration, help in removal of slough and promote angiogenesis.

5. **Hydrogel dressings-** They contain of cross-linked insoluble carboxymethylcellulose or starch polymers and water (95%). They will cause destruction of slough and necrotic tissue in the wounds by providing fluid. They provide an analgesic effect by cooling and hydrating the wound.
6. **Hydrocolloid dressing-** They are adhesive dressing which are waterproof. They help in autolytic debridement of sloughing and necrotic tissues, granulation and epithelialisation by retaining growth factors under the dressing. They absorb the exudates from the wound.
7. **Alginate dressings-** Theyare available in various forms made of calcium and sodium in different proportions. They are used in wounds with high exudates and also help in haemostasis.
8. **Mechanical device-** Negative pressure is created topically over the wound bed by using devises which create vacuum. It is effective in reducing oedema and removing exudate and provides moisture. Hyperbaric oxygen therapy is also used for treating diabetic wounds.

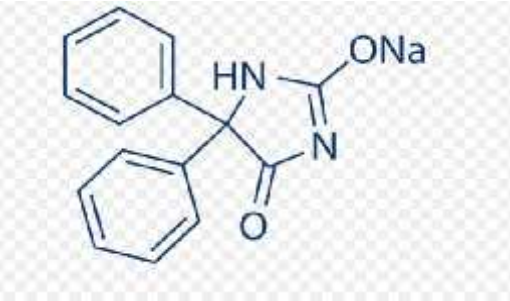
Wound classification	Choice of wound care materials	Advantages	Disadvantages
Granulating wounds	Non adherent dressing	Reduces trauma to the healing tissue Maintains a moist wound healing environment	Chance of shearing to new epithelium
	Wet to dry dressing	Promotes healing	Chance of bleeding if not soaked with saline before dressing change
	Polyurethane foam	Maintains a moist wound healing environment Promotes healing process	Chance of bleeding if not soaked before dressing change
	Topical antibacterial such as metronidazole, mupirocin, Tulle, Silver containing ointments, Acetic acid 0.5%-5% and povidone iodine	Maintains a moist wound healing environment, promotes epithelization and controls odor Effective against Gram positive cocci including MRSA. Silver sulfadiazine has broad antibacterial coverage, accelerates epithelization, and is very effective in burns. Acetic acid is very effective against Pseudomonas. Povidone iodine is very effective for gangrene as it hastens demarcation	Silver containing ointments cannot be used in Sulfa allergy patients Povidone iodine is cytotoxic to fibroblasts and delays the healing process
	Platelet derived growth factor	Faster healing and very effective	Expensive
	Hydrogel	Promotes healing	Chance of maceration and is expensive
	Hydrocolloid	Promotes healing Reduces the interval of dressing change	Chance of maceration and is expensive
Epithelizing wounds	Non adherent	Reduces trauma to the healing tissue Maintains a moist wound healing environment	Chances of shearing
	Wet to dry dressing	Promotes faster healing	Soaking of dressing is required prior to dressing change
	Topical antibacterial	As mentioned in granulating wounds	As mentioned in granulating wounds
	Epidermal growth factor	Effective and faster healing	Expensive
	Hydrogel	Effective	Chance of maceration and is expensive
	Hydrocolloid	Effective	Chance of maceration and is expensive
Cavity/Sinus wounds	Alginate	Highly absorbent and non-adherent Maintains a moist wound healing environment	Needs adequate padding and is expensive
	Hydrogel	Effective in promoting granulation tissue	Needs adequate padding and is expensive

Phenytoin sodium (diphenylhydantoin)-[37,38]

Phenytoin (diphenylhydantoin) was first made in 1908 by the German chemist Heinrich Blitz and used for the treatment of epilepsy in 1937, without the sedative effects associated with phenobarbital. It is a non sedative antiepileptic drug, most effective against partial seizures and generalized tonic clonic seizures.

Chemical structure-

Chemical structure of phenytoin is correlated to the barbiturates, but it has a 5 membered ring. The chemical name is sodium 5, 5-diphenyl-2, 4-imidazolidinedione and has the following structural formula.



The potential use of phenytoin in healing of the wound was first seen by Kimball in 1939 as some patients who were treated with phenytoin developed gingival hyperplasia. First controlled clinical trial was performed by Shapiro in 1958 and concluded that gum disease patients with surgical wounds treated previously with phenytoin orally had less or minimal inflammation, faster healing and less pain. A common adverse effect of phenytoin is gingival hyperplasia seen during treatment of convulsions. About fifty percent of patients who were treated with phenytoin developed gingival hyperplasia.[38]This stimulatory effect of phenytoin on connective tissue suggested the possibility for its use in wound healing. Phenytoin was found to increase the tensile strength of experimental skin and corneal wounds in several animal studies and faster healing was seen in dental extraction sockets. Faster fracture and periosteal healing was seen when phenytoin was administered systematically.[37]

Mechanism of action-[8, 10, 38]

1. Stimulation of fibroblast proliferation.

2. Accelerates the formation of granulation tissue.

3. Decreasing activity of collagenase, inhibition of glucocorticoid activity.

4. Antibacterial action by affecting inflammatory cells.

5. Phenytoin increases gene expression of the platelet derived growth factor beta chain of macrophage and monocytes.

6. Reduces the exudates from the wound and edema.

Many clinical trials with phenytoin used topical phenytoin for wound healing. These trials concluded that systemic absorption was not significant. In a study performed by Anstead et al., large doses of phenytoin were used to treat a large a sacrolumbar pressure ulcer. Despite of using such large doses the concentrations of phenytoin in serum was only 4.3 mg/L.

Advantages of topical phenytoin therapy-[8, 38]

1. Wound site is accessed directly without undergoing classic metabolic pathways lowering risk of side effects seen when phenytoin was used systematically for wound healing.

2. Need for antibiotic therapy is decreased as it decreases the bacterial load.

3. Possible facilitation of nerve regeneration.

4. Provides pain relief.

5. Low cost and availability as compared to other alternatives.

6. No adverse reactions were reported.

Various studies showed favorable results after using topical phenytoin for dressing of ulceration in leprosy, diabetic foot ulcers, venous ulcers, abscess cavities, burns and decubitus ulcers.[38]

A study by Muthukumarasamy MG et al. shown that the patient in whom phenytoin was used, mean healing time was 21 days and it was 45 days in patients in whom sterile occlusive dressings were used. Topical phenytoin also showed antibacterial action by showing negative wound cultures within 7-9 days.[37]

METHODSAND METHODOLOGY

This randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi over a period, from January 2019 to December 2019

Study design

The study design was a randomized controlled trial.

Study period and duration

This study was carried out for the duration of 1 year from January 2019 to December 2019.

Place

This study was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Diabetic Patients taking insulin or oral hyperglycaemic agents and suffering from diabetic foot ulcers which are not healed and for which debridement is required for healing were enrolled.

Sample size

Thepresent study was comprised of 64 Patients taking insulin or oral hyperglycaemic agents suffering from diabetic foot ulcers which are not healed and for which debridement is required for healing patients divided into two groups of 32 each.

Sample size - Total sample size of 64 cases, 32 in group A and the other 32 in group B.

Sample size calculation:

The minimum sample size (n=32) in each group is based on formula

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

$S=\frac{S_1+S_2}{2}$

S_1 =S.D of wound healing in group B =2.4

S_2=S.D of wound healing in group A=4.7

d=Mean difference=3.4

Z_α=1.96 at 5% α error

Z_β=0.842 at 80% power

There by total sample size is 64.

- The patient will be randomly divided into 2 groups.
- First group (32 pt) with phenytoin dressing.
- Second group (32 pt) with Povidone iodine dressing.
- Informed consent will be obtained from all the patients.

- Wound dressing will be changed on alternate days and the Ulcers will be observed over a period of 14 days. Ulcer area will be measured on days 1, 3, 5, 7, 10, and 14.
- If there is soakage or discharge dressing will be changed every day with water soluble Povidone Iodine and Phenytoin.
- Same antibiotic will be used for both the groups to compare the exact status of wound in both the groups; there should be no difference in wound status by using different antibiotics in both groups.

Assessment

- Ulcers are observed over a period of 14 days
- Ulcer area is measured on days 1, 3, 5, 7, 10, and 14.
- Ulcer area is calculated using graph paper by grid tracing.
- Each box of graph paper is counted and area is given in $mm^{2.}$

Selection criteria

Inclusion criteria-

- Patient suffering from non-healing diabetic foot ulcers.
- Patients with grade 1 and 2 according to Wagner's classification.

Wagner's classification-

Grade	Foot lesion
0	No open lesions or cellulitis
1	Superficial ulcer
2	Deep ulcer upto tendons and joint tissue
3	Deep ulcer with abscess, osteomyelitis and joint sepsis
4	Local gangrene forefoot or heel
5	Gangrene of entire foot

Exclusion criteria-

- Ischemic limb
- Associated osteomyelitis
- Cellulitis
- Diabetic ketoacidosis
- Exposed bone
- Hb level less than 10gm%

Ethical clearance

The study was approved from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

The eligible patients who fulfilled the selection criteria were informed in detail about the nature of the study and a written informed consent was obtained.

Method of collection of data

The demographic data was obtained through an interview. Patients were asked for the past history, ulcer duration, diabetic history and treatment history. Further these patients were subjected to clinical examination. The wound observation was performed for ulcer characteristics such as site, size, shape, edge, margin, floor, base, discharge, surrounding skin and slough / necrotic tissue. These findings were noted on a predesigned and pretested proforma.

Investigations

The patients underwent following investigations.

- Fasting blood sugar
- Complete blood count.
- HbA1c
- Renal Function test
- Urine R/M
- Wound discharge for C/S
- X-Ray foot – Antero-posterior and Lateral view (as and when required)
- Colour Doppler (as and when required)

Randomization:

The participants will be randomly allocated to both the intervention groups using computer generated random number sequence.

Sampling procedure = Computer generated randomized selection

The patient will be randomly divided into 2 groups.

- First group (32 pt) with phenytoin dressing.
- Second group (32 pt) with povidone iodine dressing.

Treatment

All the patients underwent debridement of wound. Empirical antibiotics were administered and changed to sensitive antibiotics after culture and sensitivity. The dressing was done as below.

Group A – Phenytoin dressing was done.

Group B- Povidone iodine dressing was done.

For Group A, wound was cleaned and a sterile gauze soaked in a mixture of 100 mg phenytoin sodium and 5 ml of sterile normal saline was applied over the wound. The dosage of phenytoin was increased by 50 mg for every $5cm^2$ increase in the area of ulcer.

For Group B, wound was cleaned and sterile gauze soaked with povidone iodine was applied.

- Wound dressing will be changed on alternate days and the Ulcers will be observed over a period of 15 days. Ulcer area will be measured on days 1,3, 5, 7, 10, and 14.
- If there is soakage or discharge dressing will be changed every day with water soluble Povidone Iodine and Phenytoin.
- Same antibiotic will be used for both the groups to compare the exact status of wound in both the groups; there should be no difference in wound status by using different antibiotics in both groups.

Outcome variables

- Debridement of slough/nonviable tissue, reduction in ulcer size, granulation.
- Discharge, odour, induration noted for over all response to treatment
- Ulcer was assessed by the investigator at the beginning of the study. Ulcer mapping was made and size was recorded.
- Ulcers are observed over a period of 14 days
- Ulcer area is measured on days 1,3, 5, 7, 10, and 14.
- Ulcer area is calculated using graph paper by grid tracing.
- Each box of graph paper is counted and area is given in mm^2.

Follow up

- The patients were evaluated at beginning of dressing and at two weeks.

STATISTICAL ANALYSIS

The data obtained was coded and entered in Microsoft Excel Spread sheet. Study group (Phenytoin dressing, Povidone iodine dressing) was considered as primary explanatory variable.

Wound size was considered as primary outcome parameter. Other Wound related parameters like discharge, appearance of granulation tissue and status of edges etc were considered as secondary outcome variables.

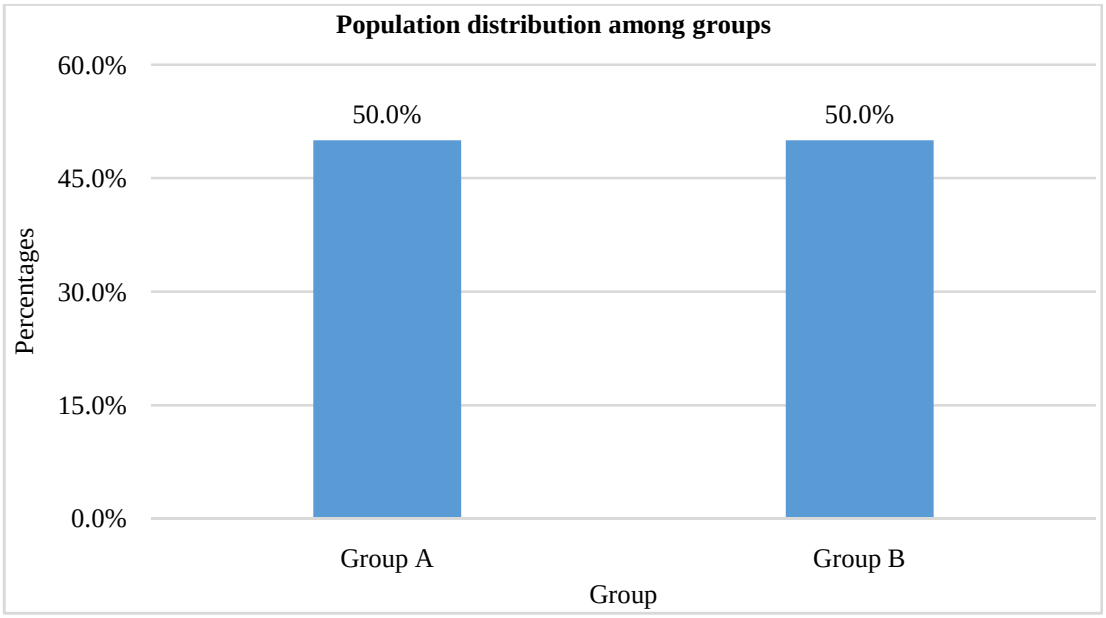
RESULTS

64 patients were included in the study

Table 2- Descriptive analysis of group in the study population (N=64)

Group	Frequency	Percentages
Group A	32	50.00%
Group B	32	50.00%

Graph 1- Bar chart of group in the study population (N=64)



The study population was divided in to 2 groups, 32(50%) participants were in group A and remaining 32(50%) participants were in group B.

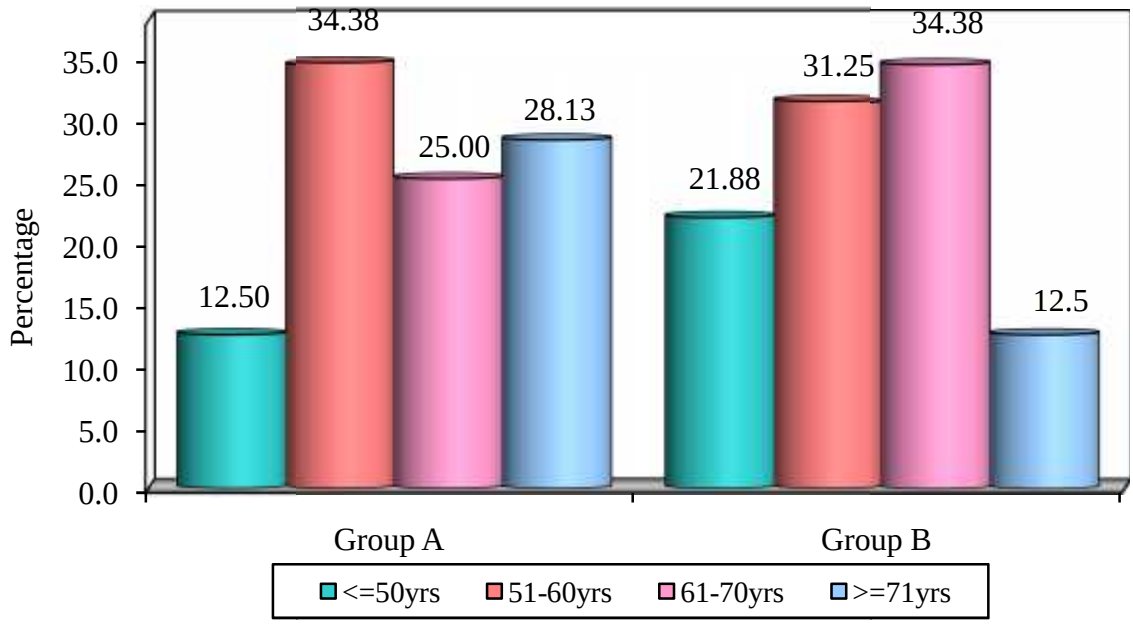
Group A - STUDY GROUP - population where phenytoin dressing done.

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

Table 3: Comparison of Group A and Group B by age groups

Age groups	Group A	%	Group B	%	Total	%
<=50yrs	4	12.50	7	21.88	11	17.19
51-60yrs	11	34.38	10	31.25	21	32.81
61-70yrs	8	25.00	11	34.38	19	29.69
>=71yrs	9	28.13	4	12.50	13	20.31
Total	32	100.00	32	100.00	64	100.00
Chi-square=3.2632 P = 0.3532						

Graph 2 :Comparison of Group A and Group B by age groups

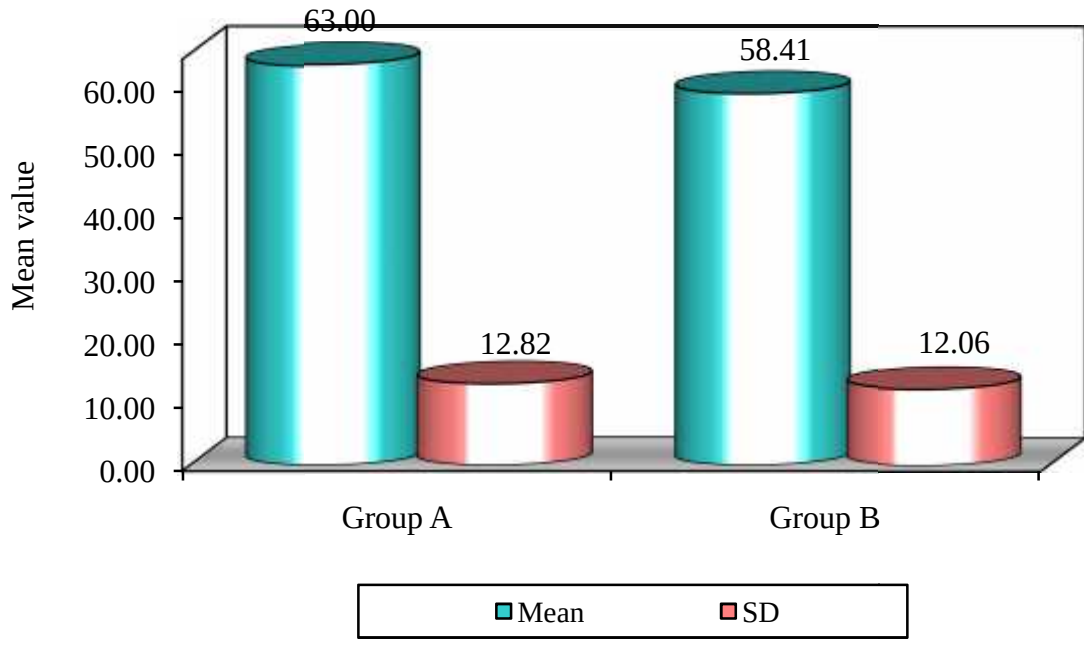


Among group A, 4 (12.50%) were aged less than 50 years, 11 (34.38%) were aged between 51to 60 years, 8 (25%) were aged between 61 to 70 years, 9 (28.13%) were aged more than 71 years. Among group B, 7 (21.88%) were aged less than 50 years, 10 (31.25%) were aged between 51 to 60 years, 11 (34.38%) were aged between 61 to 70 years, 4 (12.50%) were aged more than 71 years. There was no statistically significant differences among the groups as per age distribution were considered. (P value 0.3532).

Table 4: Comparison of Group A and Group B with mean age by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group A	63.00	12.82	2.27	1.4764	0.1449
Group B	58.41	12.06	2.13		

Graph 3: Comparison of Group A and Group B with mean age



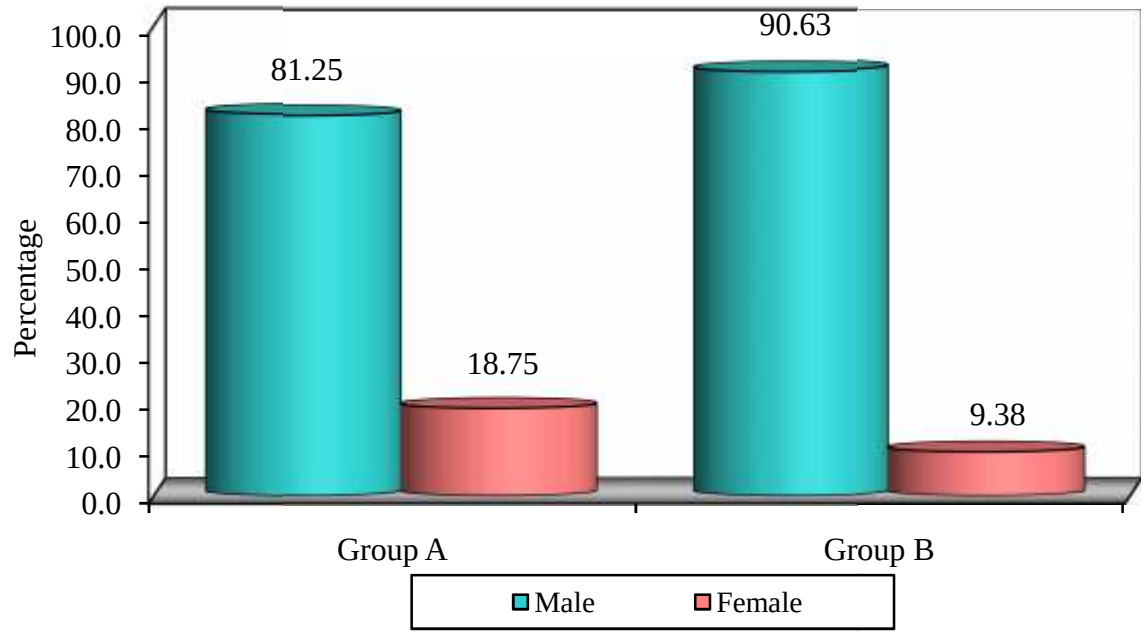
Among group A mean age was 63 and in group B it was 58.41.There was no statistically significant differences among the groups as per mean age.(P value-0.1449)

Table 5: Comparison of Group A and Group B by gender

Gender	Group A	%	Group B	%	Total	%
Male	26	81.25	29	90.63	55	85.94
Female	6	18.75	3	9.38	9	14.06
Total	32	100.00	32	100.00	64	100.00
Chi-square with Yates's correction = 0.5170 P = 0.4720						

Among the study population 55 (85.94%) participants were males and remaining 9 (14.06%) participants were females. Male preponderance is seen in this study.

Graph 4: Comparison of Group A and Group B by gender

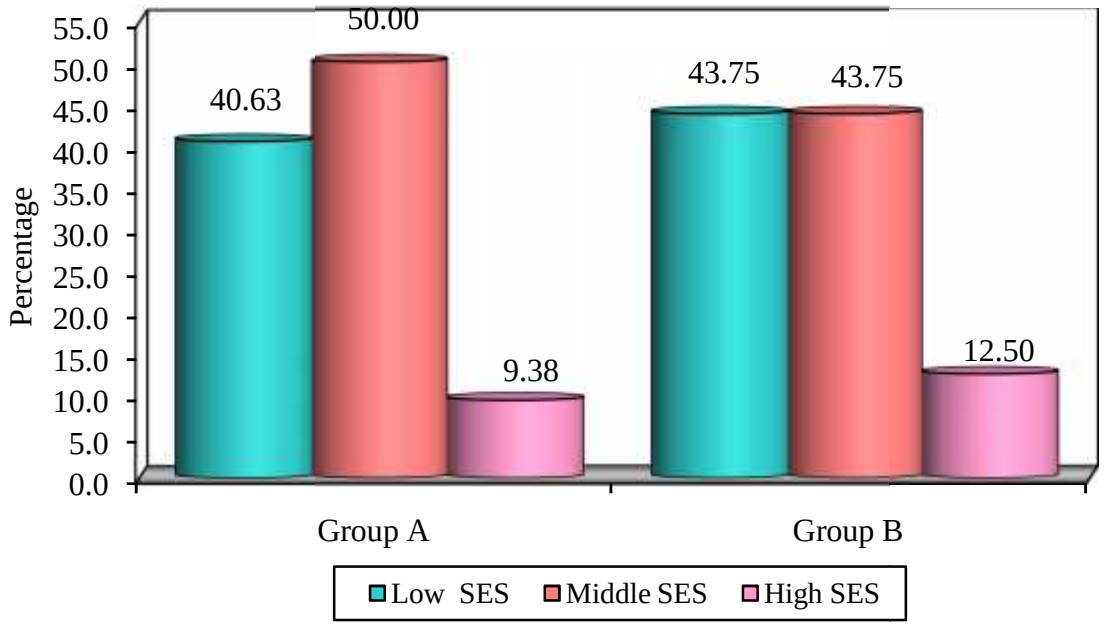


Among group A, 26 (81.25%) were males, 6 (18.75%) were females. Among group B, 29 (90.63%) were males, 3 (9.38%) were females. There was no statically significant difference among the groups as per gender distribution was considered. (P value 0.4720).

Table 6: Comparison of Group A and Group B by socio economic status

SES	Group A	%	Group B	%	Total	%
Low SES	13	40.63	14	43.75	27	42.19
Middle SES	16	50.00	14	43.75	30	46.88
High SES	3	9.38	4	12.50	7	10.94
Total	32	100.00	32	100.00	64	100.00
Chi-square = 0.3130 P = 0.8550						

Graph 5: Comparison of Group A and Group B by socio economic status

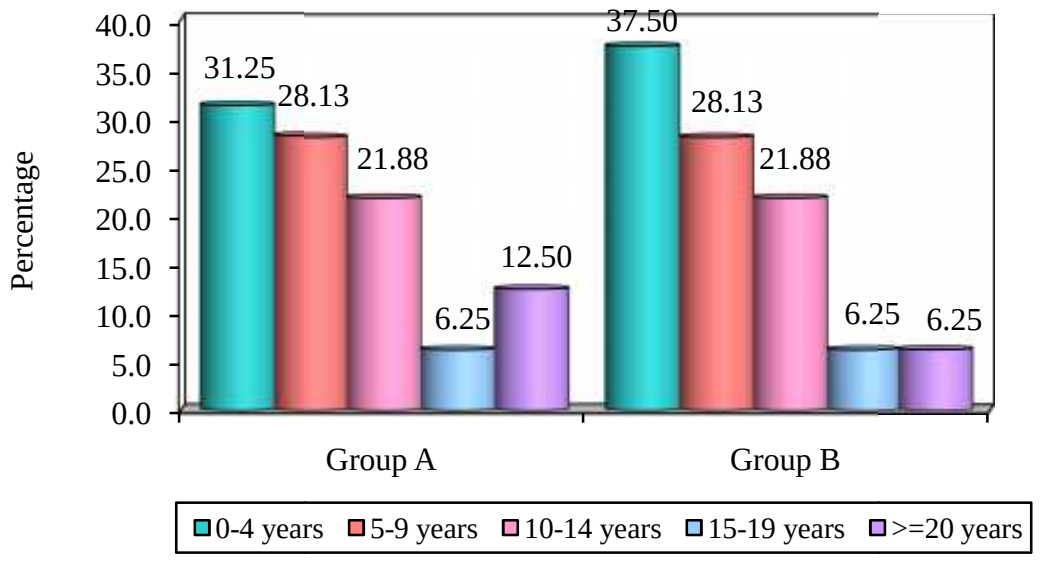


Among group A, 13 (40.63%) belonged to low socioeconomic status, 16 (50%) belonged to middle class, 3 (9.38%) belonged to high class. Among group B, 14 (43.75%) belonged to low socioeconomic status, 14 (43.75%) belonged to middle class, 4 (12.50%) belonged to high class. There was no statically significant difference among the groups as per socio economic status distribution was considered. (P value 0.8550)

Table 7: Comparison of Group A and Group B by duration of diabetes

Duration of diabetes	Group A	%	Group B	%	Total	%
0-4 years	10	31.25	12	37.50	22	34.38
5-9 years	9	28.13	9	28.13	18	28.13
10-14 years	7	21.88	7	21.88	14	21.88
15-19 years	2	6.25	2	6.25	4	6.25
>=20 years	4	12.50	2	6.25	6	9.38
Total	32	100.00	32	100.00	64	100.00
Chi-square = 0.8482 P = 0.9321						

Graph 6 :Comparison of Group A and Group B by duration of diabetes

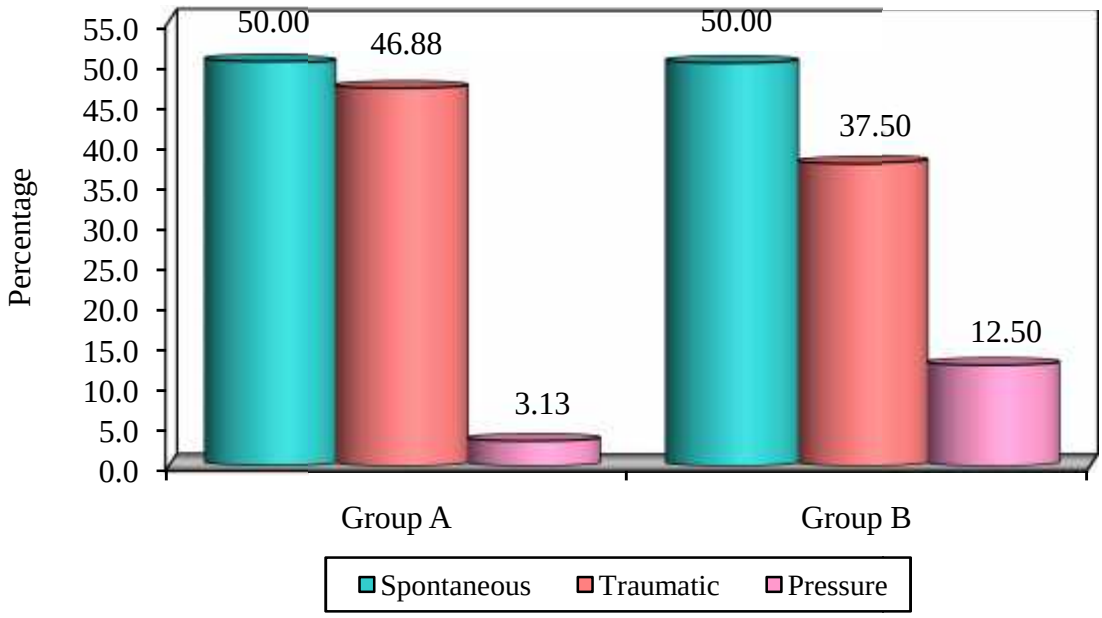


Among group A, 10 (31.25%) had diabetes duration 0 to 4 years, 9 (28.13%) had diabetes duration 5 to 9 years, 7 (21.88%) had duration 10 to 14 years, 2 (6.25%) had duration 15 to 19 years, 4 (12.50%) had duration 20 years and above. Among group B, 12 (37.50%) had diabetes duration 0 to 4 years, 9 (28.13%) had diabetes duration 5 to 9 years, 7 (21.88%) had duration 10 to 14 years, 2 (6.25%) had duration 15 to 19 years, 2 (6.25%) had duration 20 years and above. There was no statistically significant difference among two groups as per duration of diabetes was considered.(P value-0.9321)

Table 8: Comparison of Group A and Group B by onset of disease

Onset	Group A	%	Group B	%	Total	%
Spontaneous	16	50.00	16	50.00	32	50.00
Traumatic	15	46.88	12	37.50	27	42.19
Pressure	1	3.13	4	12.50	5	7.81
Total	32	100.00	32	100.00	64	100.00
Chi-square = 2.1330 P = 0.3440						

Graph 7: Comparison of Group A and Group B by onset of disease

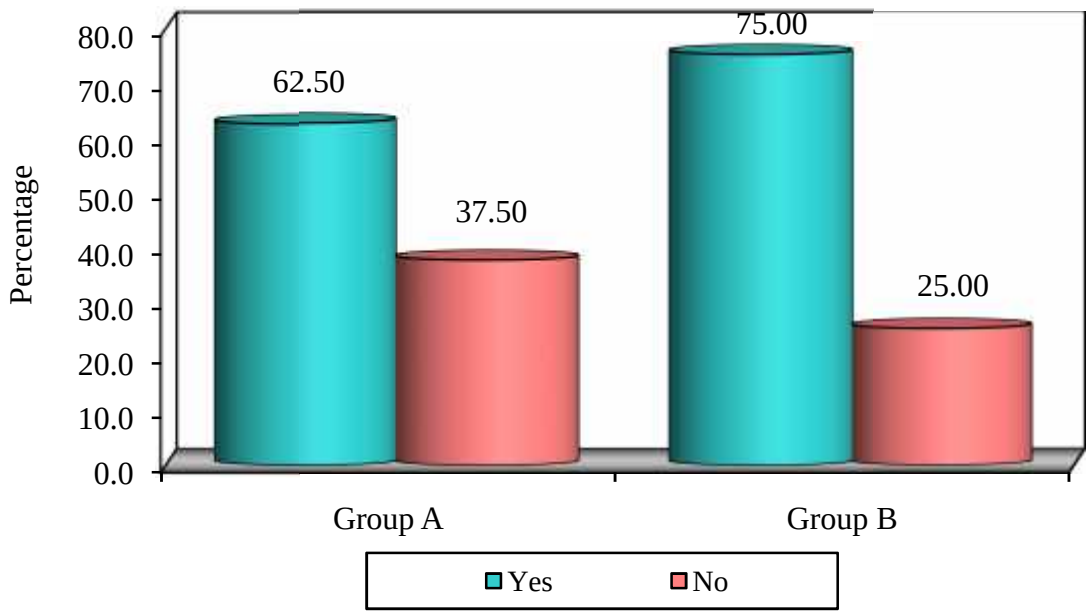


Among group A**,** 16 (50%) had spontaneous onset, 15 (46.88%) had traumatic onset, 1 (3.13%) had pressure onset. Among group B, 16 (50%) had spontaneous onset, 12 (37.50%) had traumatic onset, 4 (12.50%) had pressure onset. There was no statistically significant difference among two groups as per mode of onset was considered.(P value 0.3440).

Table 9: Comparison of Group A and Group B by status of neuropathy

Status of neuropathy	Group A	%	Group B	%	Total	%
Yes	20	62.50	24	75.00	44	68.75
No	12	37.50	8	25.00	20	31.25
Total	32	100.00	32	100.00	64	100.00
Chi-square = 1.1643 P = 0.2812						

Graph 8 : Comparison of Group A and Group B by status of neuropathy

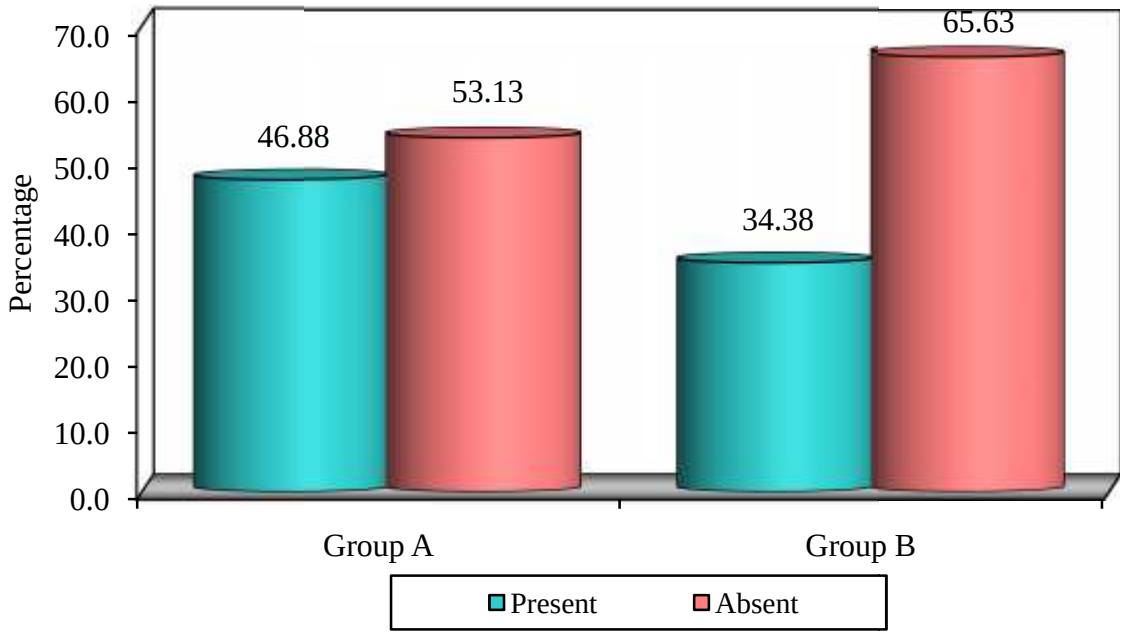


Among group A, 20 (62.50%) had neuropathy. Among group B, 24 (75%) had neuropathy. There was no statistically significant difference among the groups as per neuropathy distribution was considered. (P value 0.2812).

Table 10: Comparison of Group A and Group B by status of hypertension

Status of hypertension	Group A	%	Group B	%	Total	%
Present	15	46.88	11	34.38	26	40.63
Absent	17	53.13	21	65.63	38	59.38
Total	32	100.00	32	100.00	64	100.00
Chi-square = 1.1643 P = 0.2812						

Graph 9: Comparison of Group A and Group B by status of hypertension

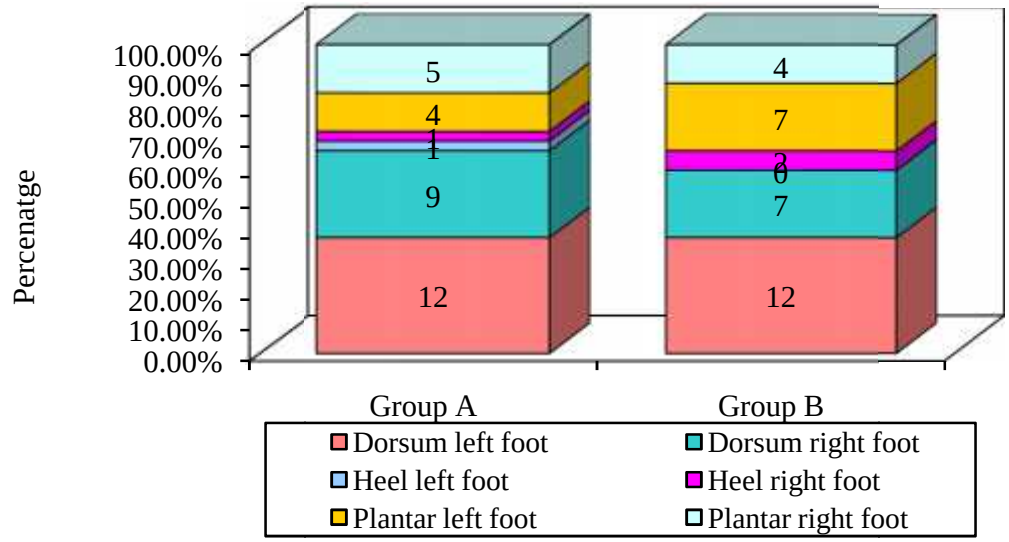


Among group A, 15 (46.88%) had hypertension. Among group B, 21(65.63%) had hypertension. There was no statistically significant difference among the groups as per hypertension was considered.(P value 0.2812).

Table 11: Comparison of Group A and Group B by sites

Sites	Group A	%	Group B	%	Total	%
Dorsum left foot	12	37.50	12	37.50	24	37.50
Dorsum right foot	9	28.13	7	21.88	16	25.00
Heel left foot	1	3.13	0	0.00	1	1.56
Heel right foot	1	3.13	2	6.25	3	4.69
Plantar left foot	4	12.50	7	21.88	11	17.19
Plantar right foot	5	15.63	4	12.50	9	14.06
Total	32	100.00	32	100.00	64	100.00
Chi-square = 2.5130 P = 0.7750						

Graph 10:Comparison of Group A and Group B by sites

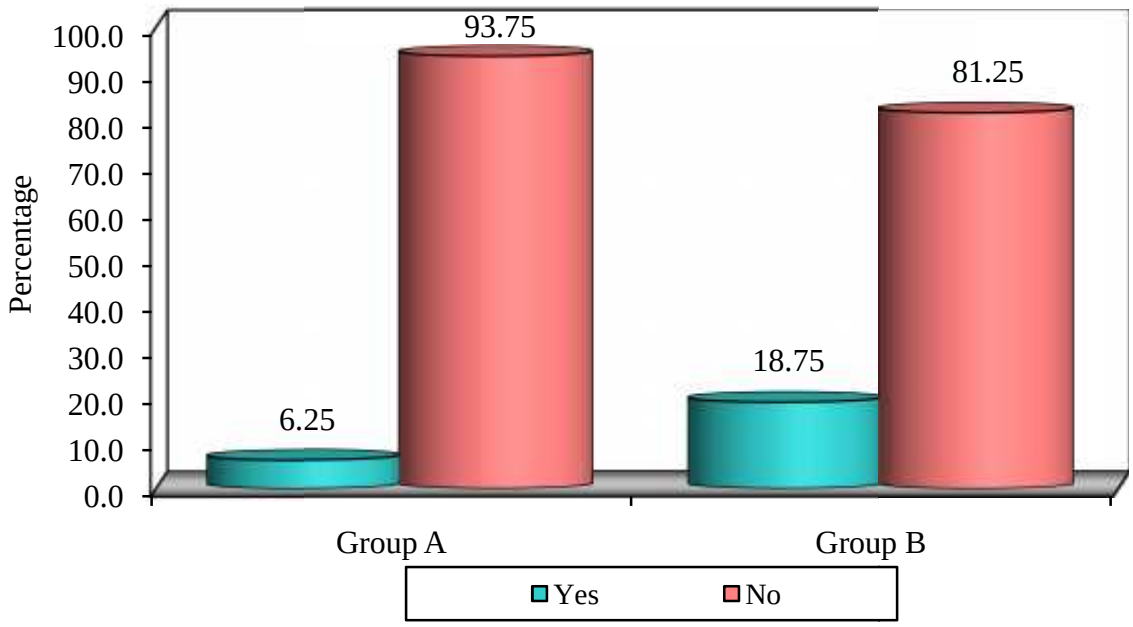


Among group A, 12 (37.50%) had site of ulcer at dorsum of left foot, 9 (28.13%) had at dorsum of right foot, 1 (3.13%) had at heel of left foot, 1 (3.13%) had at heel of right foot, 4 (12.50%) had at plantar aspect of left foot, 5 (15.63%) had at plantar aspect of right foot. Among group B, 12 (37.50%) had site of infection at dorsum left foot, 7 (21.88%) had at dorsum right foot, 2 (6.25%) had at heel of right foot, 7 (21.88%) had at plantar left foot, 4 (12.50%) had at plantar right foot. There was no statistically significant difference among the groups as per site of ulcer was considered. (P value 0.7750).

Table 12: Comparison of Group A and Group B by status of slough at day 14

Slough at day 14	Group A	%	Group B	%	Total	%
Yes	2	6.25	6	18.75	8	12.50
No	30	93.75	26	81.25	56	87.50
Total	32	100.00	32	100.00	64	100.00
Chi-square with Yates's correction = 1.2860 P = 0.2571						

Graph 11: Comparison of Group A and Group B by status of slough at day 14



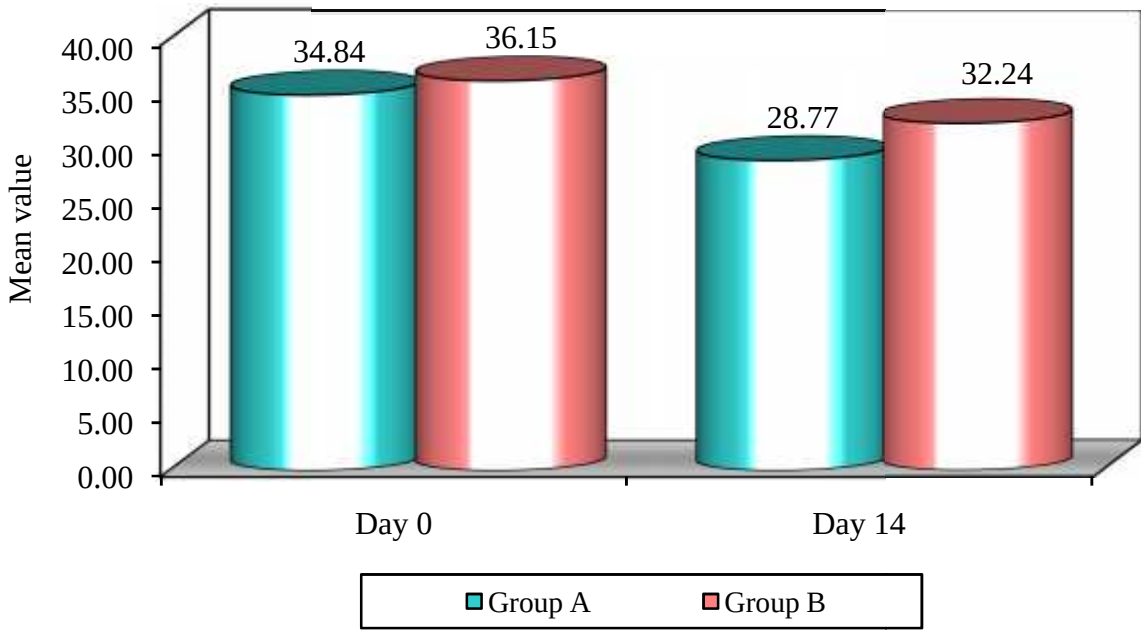
Among group A 2 (6.25%) had slough on day 14 and in group B 6 (18.75) had slough on day 14. There was no statistically significant difference among the groups as per slough on day14. (P value-0.2571)

Table 13: Comparison of Group A and Group B with Area of Ulcer on day 0 and day 14 by independent t test

Time points	Groups	Mean	SD	SE	t-value	P-value
Day 0	Group A	34.84	22.18	3.92		
	Group B	36.15	17.12	3.03	-0.2644	0.7924
Day 14	Group A	28.77	20.02	3.54		
	Group B	32.24	16.45	2.91	-0.7585	0.4510
Reduction	Group A	6.07	3.96	0.70		
	Group B	3.91	1.54	0.27	2.8780	0.0055*

*p<0.05

Graph 12: Comparison of Group A and Group B with area of ulcer on day 0 and day 14



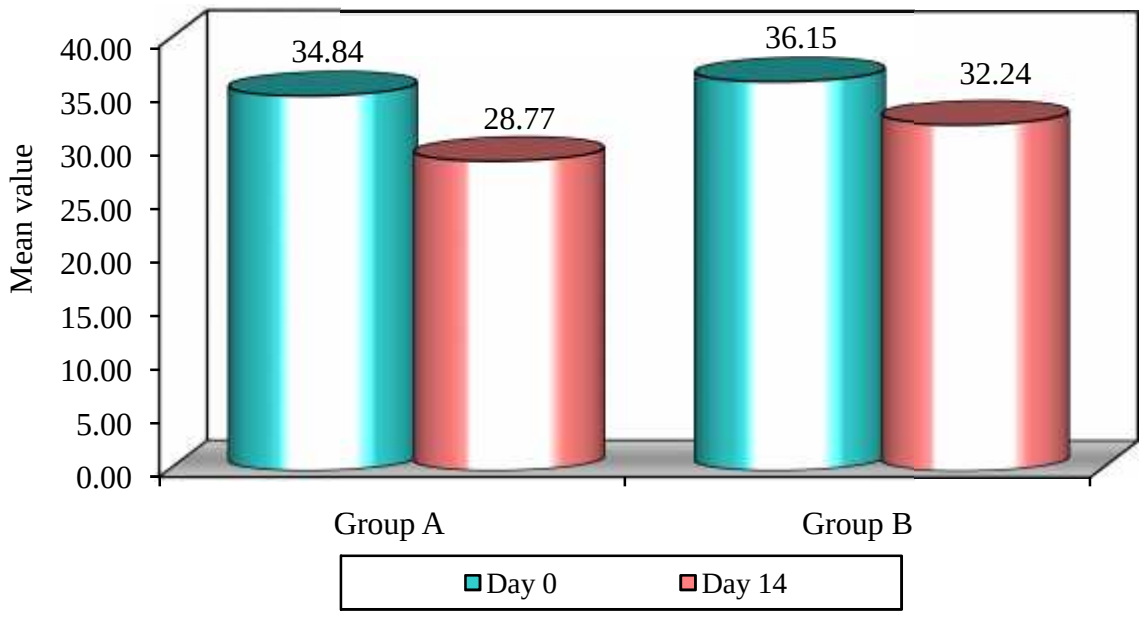
The mean initial ulcer area (D0) in group A was 34.84; it was 36.15 in group B. The difference in area D0 between 2 groups was not significant. (P value 0.7924). Mean initial ulcer area between two groups is similar.

Table 14: Comparison of mean area of ulcer on day 0 and day 14 in Group A and Group B by dependent t test

Groups	Time points	Mean	Std.Dv.	Mean Diff.	SD Diff.	t-value	P-value
Group A	Day 0	34.84	22.18	6.08	3.97	8.6652	0.0001*
	Day 14	28.77	20.02				
Group B	Day 0	36.15	17.12	3.91	1.54	14.3751	0.0001*
	Day 14	32.24	16.45				

*p<0.05

Graph 13: Comparison of mean area of ulcer on day 0 and day 14 in Group A and Group B



The mean final ulcer area (D14) in group A was 28.77; it was 32.24 in group B. The difference in area on D14 between 2 groups was significant. (P value 0.0001). Mean final ulcer area between two groups was statistically significant.

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

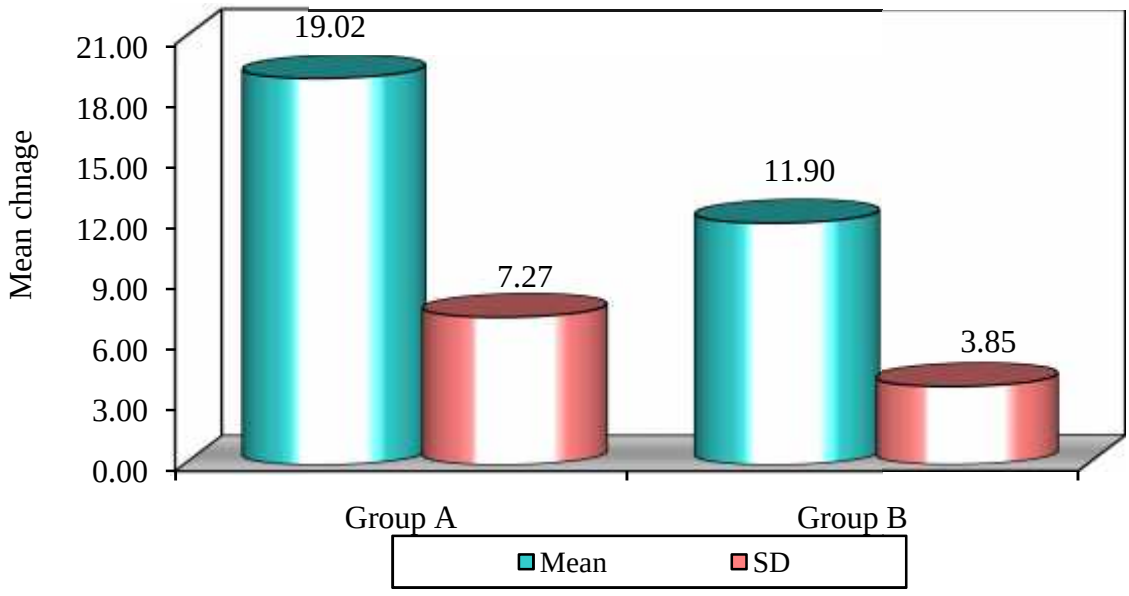
% Reduction in wound area = $\frac{x-y}{x} x100$

Table 15: Comparison of Group A and Group B with mean percent reduction in area of ulcer from day 0 and day 14 by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group A	19.02	7.27	1.29	4.8964	0.0001*
Group B	11.90	3.85	0.68		

*p<0.05

Graph 14: Comparison of Group A and Group B with mean percent reduction in area of ulcer from day 0 and day 14



The mean percentage reduction in area in group A was 19.02 ± 7.27; it was 11.90 ± 3.85 in group B. The difference in percentage reduction in area between 2 groups was statistically significant. (P value<0.001). Mean percentage reduction in ulcer area was significant in Group A compared to Group B. That is, ulcer healing was good in group where phenytoin was used for dressing.

DISCUSSION

According to International Diabetic Federation (IDF) people affected by diabetesin the world are approximately half a billion.Ninth edition of IDF Diabetes Atlas states that diabetes is one of the fastest growing global health emergencies of the 21st century.[5]

Many complicationsoccur due to hyperglycemia.[3,13] In a patient with diabetes complications like neuropathy and PAD will lead to foot ulceration.[3,19,20] The risk of ulceration and amputation among diabetics increases 2 to 4 times with advancement of age and increased duration of DM. Diabetic foot ulcer contributes for about two thirds of all non-traumatic amputations.[37] A lower limb is amputated every 30 sec as a consequence of diabetes or its complications mostly due to infection.[2]Timely management can reduce amputations by up to 70% in patients suffering from diabetic foot.[37]

Debridement along with regular dressings plays a crucial role in woundhealing in diabetics. Now days many expensive topical molecular factors for wound healing have been introduced. The effectiveness of those agents is still questionable and the cost of these molecular factors is high. Phenytoin is easy to use, cheap and acquirable easily for medical practice.[8]This study done on DFU compared the efficiency of topical phenytoin dressing with povidone iodine dressing.

This randomized control study was done under the department of general surgery at KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru nagar. Belagavi, between January 2019 to December 2019. A total number of 64 patients with diabetic foot ulcers (Wagner's grade 1 and 2) satisfying the selection criteria and willing to participate in the study were included for study.

These patients are divided into two groups of 32 each, to receive treatment with phenytoin dressing (Group A) and povidone iodine dressing (Group B).

In our study, in the study population, 11 (17.19%) were aged less than 50 years, 21 (32.81%) were aged between 51to 60 years, 19 (29.69%) were aged between 61 to 70 years, 13 (20.31%) were aged more than 71 years. Maximum number of patients who participated in our study were between the age group of 51 to 70 years. Among group A mean age was 63 and in group B it was 58.41.There was no statistically significant differences among the groups as per mean age.(P value-0.1449)

In our study, among the study population 55 (85.94%) participants were males and remaining 9 (14.06%) participants were females. Male preponderance was seen in our study. Among group A, 26 (81.25%) were males, 6 (18.75%) were females. Among group B, 29 (90.63%) were males, 3 (9.38%) were females. There was no statically significant difference among the groups as per gender distribution was considered. (P value 0.4720)As reported by the previous studies males are more prone for diabetic foot ulceration compared to females, our study results were consistent with them.

Among group A, 13 (40.63%) belonged to low socioeconomic status, 16 (50%) belonged to middle class, 3 (9.38%) belonged to high class. Among group B, 14 (43.75%) belonged to low socioeconomic status, 14 (43.75%) belonged to middle class, 4 (12.50%) belonged to high class. There was no statically significant difference among the groups as per socio economic status distribution was considered. (P value 0.8550). In our study group 27 (42.19%) belonged to low socioeconomic status, 30 (46.88%) belonged to middle class, 7 (10.94%) belonged to high class. A study by Vibha et al. concluded that low and middle socio-economic status was a risk

factor for development of diabetic foot ulcers; our study results were consistent with them[40].

Among the study population 32 (50%) had spontaneous onset of ulcer, 27 (42.19) had traumatic onset, 5 (7.81%) had pressure onset. A study by Edo, A et al stated that spontaneous blisters are the common risk factors for development of diabetic foot ulcers, fifty per cent of our study population had spontaneous onset of ulcer.[42]Our findings in the study were in accordance with them. Among group A**,** 16 (50%) had spontaneous onset, 15 (46.88%) had traumatic onset, 1 (3.13%) had pressure onset. Among group B, 16 (50%) had spontaneous onset, 12 (37.50%) had traumatic onset, 4 (12.50%) had pressure onset. There was no statistically significant difference among two groups as per mode of onset was considered. (P value 0.3440).

Among group A, 12 (37.50%) had site of ulcer at dorsum of left foot, 9 (28.13%) had at dorsum of right foot, 1 (3.13%) had at heel of left foot, 1 (3.13%) had at heel of right foot, 4 (12.50%) had at plantar left foot, 5 (15.63%) had at plantar aspect of right foot. Among group B, 12 (37.50%) had at dorsum of left foot, 7 (21.88%) had at dorsum of right foot, 2 (6.25%) had at heel of right foot, 7 (21.88%) had at plantar aspect of left foot, 4 (12.50%) had at plantar aspect of right foot. There was no statistically significant difference among the groups as per site of ulcer was considered. (P value 0.7750).

Among group A, 10 (31.25%) had diabetes duration of 0 to 4 years, 9 (28.13%) had diabetes duration of 5 to 9 years, 7 (21.88%) had duration of 10 to 14 years, 2 (6.25%) had duration of 15 to 19 years, 4 (12.50%) had duration of 20 years and above. Among group B, 12 (37.50%) had diabetes duration of 0 to 4 years, 9 (28.13%) had diabetes duration of 5 to 9 years, 7 (21.88%) had duration of 10 to 14 years, 2 (6.25%) had duration of 15 to 19 years, 2 (6.25%) had duration 20 years and

above. There was no statistically significant difference among two groups as per duration of diabetes was considered.(P value-0.9321)

A study by Abbott, C et al. stated that more than 80 per cent of patients with diabetic foot preceded with neuropathy.[41]In our study 44 (68.75%) patients had neuropathy, our study results were consistent with the study by Abbott, C et al. Among group A, 20 (62.50%) had neuropathy. Among group B, 24 (75%) had neuropathy There was no statistically significant difference among the groups as per neuropathy distribution was considered. (P value 0.2812).

In our study 26 (40.63%) had hypertension and 38 (59.38%) did not have hypertension. Previous studies stated that hypertension is a risk factor for development of foot ulcer in diabetics. Our study results were not consistent with them as 59.38% of our study population were non hypertensives. Among group A, 15 (46.88%) had hypertension. Among group B, 21 (65.63%) had hypertension. There was no statistically significant difference among the groups as per hypertension was considered.(P value 0.2812).

Most of our study results were consistent with previous studies, so age group, sex, socioeconomic status, site of ulcer, onset of ulcer, neuropathy and hypertension can be considered as risk factors for development of foot ulcers in people with diabetes. 'P' value for the above mentioned factors was less than 0.05, ruling out bias in our study outcome.

Among group A 2 (6.25%) had slough on day 14 and in group B 6 (18.75) had slough on day 14. There was no statistically significant difference among the groups as per slough on day 14. (P value-0.2571)

In our study, the mean initial ulcer area (D0) in group A was 34.84; it was 36.15 in group B. The difference in area D0 between two groups was statistically not

significant. (P value 0.7924). Mean initial ulcer area between two groups is similar. The mean final ulcer area (D14) in group A was 28.77, it was 32.24 in group B, and the difference in area D14 between two groups was statistically significant. (P value 0.0001). Mean final ulcer area between two groups was statistically significant. The mean percentage reduction in area in group A was 19.02 ± 7.27; it was 11.90 ± 3.85 in group B. The difference in percentage reduction in area between two groups was statistically significant. (P value <0.001).These findings suggest that dressing with topical application of phenytoin favours ulcer healing compared to dressing with povidone iodine.

A study by El-Nahas M et al. concluded that topical phenytoin will amplify wound healing in diabetics with foot ulcers due to neuropathy and it is safe.[43]

A study by Bhradva P B et al. showed that the group in which phenytoin was used, mean rate of formation of healthy granulation tissue was 60.71%, mean hospital stay was 23.96 days and rate of negative culture sensitivity was 54%. The group in which povidone iodine was used showed mean formation of healthy granulation tissue of 11%, and mean hospital stay was 35 days and rate negative culture sensitivity was 18%.[10]

In a study by kumar, R.A.S. et al. among 50 patients with non healing diabetic ulcers topical phenytoin was used and observation was done over a period six months and nine days. 43 patients showed rapid formation of granulation tissue and early coverage of the wound. These patients also underwent skin grafting and wound healing was complete, the patients in the control group also underwent skin grafting who took around 8 weeks and recurrences of the ulcers were reported. Hospital stay was also reduced in the study group. Topical phenytoin was also effective in the ulcers of other aetiologies; it is inexpensive and easily available than other newer

forms of topical applications. No side effects were reported as phenytoin was topically used and safer serum levels of phenytoin were seen.[44]

A study by Rhodes, R. et al. Topical phenytoin treatment of stage 2 decubitus ulcers in the elderly, concluded that in patients with topical phenytoin therapy wound healing and granulation tissue formation took less time compared to application of topical triple antibiotic or Duoderm dressing's applications. Healthy granulation tissue was seen in 2 to 7 days in patients with topical phenytoin therapy.[45]

A randomized control study conducted by Gunasekaran, V. et al. on the "efficacy of phenytoin dressing in healing of diabetic ulcer" stated that in phenytoin group rate of formation of granulation tissue was 90.36% and was significant statistically compared with control group which was 82.03%. Fifty percent negative wound culture was seen in phenytoin group and twenty four percent was seen in control group. Mean hospital stay was also less in the patients in phenytoin group.[46]

Overall the present study has shown that use of topical phenytoin dressing for patients with diabetic foot ulcers had beneficial results in terms of percentage reduction in area of the wound compared to povidone iodine. Phenytoin is inexpensive and easily available. No side effects were seen in the study population who were treated with topical phenytoin.

LIMITATIONS OF STUDY-

Our study population was 64 and it was conducted in a single center. Further multicentric studies with large sample size are required to confirm these observations.

CONCLUSION

In our present study we conclude that use of topical phenytoin dressing for patients with diabetic foot ulcers had beneficial results in progress of ulcer healing in the terms of reduction in area of the wound and compliance of the patients was better with topical phenytoin dressing compared withpovidone iodine dressing. Thus, topical phenytoin wound dressing can be considered as a superior option in the management of diabetic ulcers. But further studies with larger population are required to confirm these observations.

SUMMARY

Phenytoin is an anti epileptic which is in use for the treatment of epilepsy since 1937. Inspite of the better wound healing properties and easy availability phenytoin is not used widely for dressing of diabetic foot ulcers. This made us undertake the present study.

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

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

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

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

In our study mean final ulcer area between two groups was statistically significant. The mean percentage reduction in area in group A was 19.02 ± 7.27; it was 11.90 ± 3.85 in group B. The difference in percentage reduction in area between two groups was statistically significant.

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

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ANNEXURE I

CONSENT STATEMENT

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

- I confirm that I have read and understood the information sheet forthe above study and have had the opportunity to ask questions.
- I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without mymedical care or legal rights being affected.
- I understood that sponsor of the clinical trial, others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understood that my identity will not be revealed in any information released to third parties or published.
- I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes.
- I agree to take part in the above study.

Subject's name:

Signature / left thumb impression of subject: Date:

Name of person obtaining informed consent:

Signature of person obtaining informed consent:

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

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

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

Name of the patient:

Name of representative:

Relationship to the patient:

Signature of representative:

Date:

Impartial witness declaration:

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

Name of impartial witness:

Date – **Signature:**

ANNEXURE II.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/ 01 **Date: 24/11/2018**

To,

REG.NO-BH0118005
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 **"TOPICAL PHENYTOIN SODIUM DRESSING IN DIABETIC ULCER – A COMPARATIVE STUDY WITH POVIDONE IODINE DRESSING: A 1 YEAR RANDOMIZED CONTROLLED TRAIL",** 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.

9

ANNEXURE III - PROFORMA

Group: I.D NO:

1.Name of the patient :_____

2.Age :

3.Gender : 1. Male 2. Female

4.DOA :

5.DOD :

6.Date of interview :

7.IP no :

8.Address : 1.Belagavi 2.Outside Belagavi

9.Phno :

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

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

5-Degree and above

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

Screening -

13.H/O diabetes : 1-Yes 2-No

Type 1	
Type 2	

14.If yes, type of diabetes :

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

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

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

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

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

Data collection instrument :

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

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

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

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

5.Duration of diabetes-

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

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

8.Complication:

	Yes	No
Neuropathy		
Vasculopathy		

9.H/O hypertension-1.Yes
2.No

10.Medical history:

	Yes	No
Peripheral neuropathy		
Nephropathy		
PVD		
CVD		

11.Amputaion 1.Yes
2.No
If yes, DATE
REASON

Examination:

1.

Height	Weight	BMI

2.

Pulse rate	Blood pressure	Temperature	Respiratory Rate

3. Foot Deformity:

1- Toe deformity 2 – Charcot's foot

4. Wound Observations:

	Day 0	Day 7	Day 14
• Site of ulcer			
2. Size of ulcer			
• Shape 1 – oval 2 – circular 3 – irregular			
• Margin • Regular • Irregular			
• Edge • Indistinct, diffuse • Attached to base • Not attached, hanging • Rolled in • Hyperkeratotic/ callous like • Fibrotic/ scarred			
• Floor • Red granulation tissue • Pale granulation tissue • Slough/necrotic tissue			
• Base • Fascia, tendons • Soft tissue • Bone			
• Discharge • None • Serous • Purulent • Serosanguinous • Sero-purulent			
• Surrounding skin • Edema • Eczema • Pigmented • Normal			

5.Wagner Grading:

0	
1	
2	
3	
4	
5	

6. Peripheral pulsations of lower limb:

	Right lower limb	Left lower limb
• Dorsalis pedis		
• Anterior tibial		
• Posterior tibial		
• Popliteal		
• 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.Slough area over ulcer:

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

3. 1.Wound area on D_0 =
2.Wound area on D_{14} =

4. Wound area reduction =
(Area on D_0-Area on D_{14})

Percentage wound area reduction = ×100

Percentage rate of wound area reduction =

5. Slough area on D_0 =

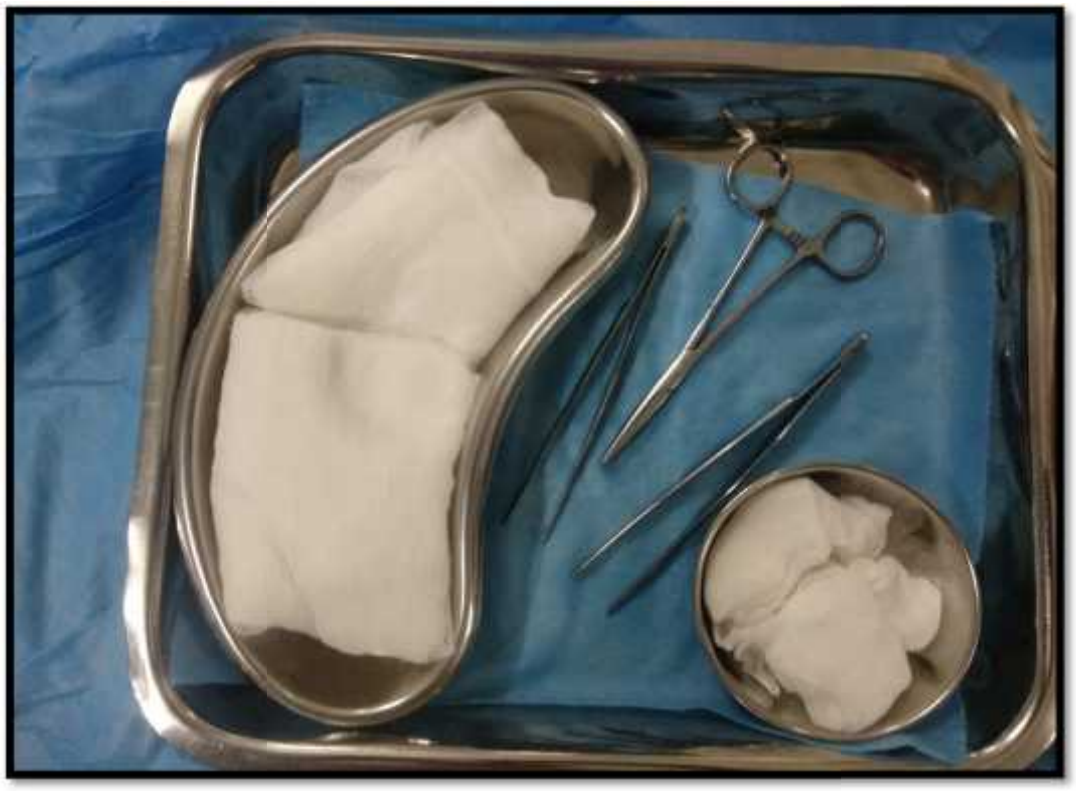
Slough area on D_{14} =

ANNEXURE IV - KEY TO MASTERCHART

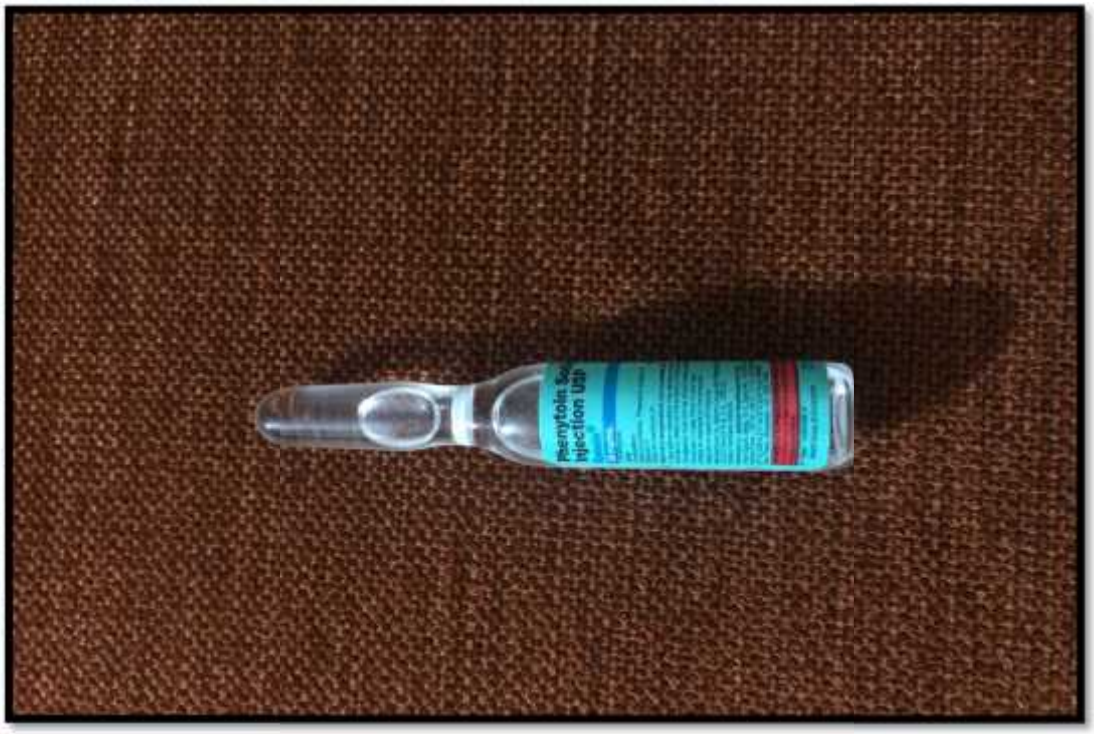
1. S.NO - Serial number
2. IP NO - Inpatient number
3. SEX - 1. Male 2. Female
4. SOCIOECONOMIC STATUS – 1. Low 2. Middle 3.High
5. DURATION OF DIABETES – 1.0-4 years 2.5-9 years 3.10-14 years 4.15-19 years 5.>/=20 years
6. ONSET – 1.Spontaneous 2. Traumatic 3. Pressure
7. NEUROPATHY - 1.Yes 2.No
8. HYPERTENSION – 1.Yes 2.No
9. SITE – DRF Dorsum right foot, PRF Plantar right foot, DLF Dorsum left foot, PLF Plantar left foot, HRF Heel right foot, HLF Heel left foot
10. SLOUGH- 1.Yes 2.No

	GROUP A PHENYTOIN													
S.NO	IP NO	AGE	SEX	SOCIOECONOMIC STATUS	DURATION OF DIABETIS	ONSET	NEUROPATHY	HYPERTENSION	SITE	AREA D0	AREA D14	REDUCTION IN AREA	%REDUCTION IN AREA	SLOUGH D 14
1	925335	51	2	2	2	1	1	1	DLF	85.5	81.2	4.3	5.0292	1
2	926410	61	1	1	1	1	2	2	PRF	33.6	31.2	2.4	7.1428	2
3	926679	73	1	1	4	2	1	2	DLF	24.6	19.8	4.8	19.5121	2
4	955800	70	1	1	1	2	2	2	PRF	75.2	68.1	7.1	9.4414	1
5	928806	58	1	2	1	1	2	2	DRF	76.9	67.4	9.5	22.3537	2
6	929109	51	1	2	2	1	2	2	PRF	5.5	4.1	1.4	25.4545	2
7	928269	50	1	1	1	2	1	2	DRF	7	5.8	1.2	17.1428	2
8	929815	33	1	2	2	1	2	2	DRF	4.3	3.4	0.9	20.9302	2
9	931897	56	1	2	5	2	1	1	PLF	22.6	19.1	3.5	15.4867	2
10	938660	60	2	1	3	1	2	2	DLF	40.1	34.6	5.5	13.7157	2
11	940349	89	1	3	5	2	1	1	DLF	17.2	13.1	4.1	24.1898	2
12	940119	75	1	2	5	2	1	1	PRF	72.5	65.6	6.9	9.5172	2
13	954277	59	1	2	1	2	2	2	DRF	23.5	19.2	4.3	18.2978	2
14	949294	40	1	1	2	1	2	1	DLF	18.2	13.8	4.4	24.3956	2
15	946127	64	1	2	2	2	2	1	DLF	38.7	31.2	7.5	19.3798	2
16	945128	54	1	1	2	2	2	2	DRF	27.3	21.6	5.7	20.8791	2
17	953338	67	1	2	1	1	2	2	DLF	17.2	16.1	1.1	6.39534	2
18	954944	75	2	1	1	1	2	1	DRF	64.8	53.2	11.6	17.9012	2
19	959262	77	1	2	3	1	1	1	DRF	33.8	29.2	4.6	13.6094	2
20	962894	68	1	3	3	2	1	1	PRF	54.7	46.2	8.5	15.5393	2
21	967318	65	2	3	2	1	2	1	HLF	7.9	6.6	1.3	16.4556	2
22	940349	62	1	2	3	1	1	1	DLF	44.6	30.2	14.4	32.2869	2
23	983122	72	1	1	5	2	1	2	DLF	28.4	21.2	7.2	25.3521	2
24	988809	50	1	2	2	1	2	2	PLF	22.6	17.2	5.4	23.8938	2
25	988727	56	1	2	3	2	1	1	DRF	38.7	31.8	6.9	17.8294	2
26	992463	59	1	1	1	1	2	1	HRF	54.6	42.2	12.2	22.7106	2
27	971730	91	2	2	4	1	2	1	DLF	34.5	24.4	10.1	29.2753	2
28	971956	54	1	1	1	2	2	2	PLF	28.2	22.4	5.8	20.5673	2
29	966607	56	1	2	2	3	2	2	PLF	18.8	14.6	4.2	22.3404	2
30	963755	75	1	1	3	1	2	2	DLF	8.2	7.4	0.8	9.756	2
31	962627	80	1	1	3	2	1	1	DLF	48.4	32.4	16	33.0578	2

GROUP B BETADINE														
S.NO	**IP.NO**	**AGE**	**SEX**	**SOCIOECONOMIC STATUS**	**DURATION OF DIABETIS**	**ONSET**	**NEUROPATHY**	**HYPERTENSION**	**SITE**	**AREA D0**	**AREA D14**	**REDUCTION IN AREA**	**%REDUCTION IN AREA**	**SLOUGH D 14**
1	921551	48	1	1	1	1	2	2	PLF	9.1	8.2	0.9	9.8901	2
2	974409	56	2	2	2	1	2	2	DLF	24.3	19.4	4.9	20.164	2
3	934419	62	1	2	3	1	1	2	DLF	31.6	28.8	2.8	8.8607	2
4	945872	45	1	1	3	2	2	1	DRF	48.4	45.1	3.3	6.8181	1
5	926266	38	1	2	1	1	2	2	HRF	33.2	29.3	3.9	11.7469	2
6	929368	53	1	1	1	1	1	1	PLF	38.8	35.9	2.9	7.4742	2
7	928973	75	1	1	5	2	1	1	DLF	26.4	22.2	4.2	15.909	2
8	942358	62	1	1	1	2	2	2	PLF	42.5	39.8	2.7	6.3529	2
9	924406	65	1	1	2	2	2	2	PLF	54.2	48.6	5.6	10.3321	1
10	935617	53	1	1	3	1	2	2	DRF	36.8	32.1	4.7	12.7717	2
11	949979	54	1	2	3	2	2	1	DLF	28.6	24.3	4.3	15.0349	2
12	950953	36	2	2	1	2	2	2	PRF	18.4	16.2	2.2	11.9565	2
13	964152	38	1	1	1	1	2	2	DLF	31.8	27.9	3.9	12.2641	2
14	969075	65	2	1	3	2	1	1	DLF	48.1	44.8	3.3	6.8607	1
15	971715	65	1	2	2	3	2	1	DRF	16.9	14.2	2.7	15.9763	2
16	974706	78	1	2	3	1	1	1	PRF	34.6	30.8	3.8	10.9826	2
17	968058	59	1	3	2	3	2	2	DLF	64.2	55.6	8.6	13.3956	2
18	977276	64	1	2	2	1	2	2	PRF	42.9	38.1	4.8	11.1888	1
19	978763	51	1	2	1	2	2	2	DLF	32.4	28.3	4.1	12.6543	2
20	979109	63	1	2	1	1	2	2	PLF	46.8	40.5	6.3	13.4615	2
21	983158	78	1	1	4	2	1	1	DRF	76.4	73.1	3.3	4.3193	1
22	981952	55	1	1	2	1	2	2	DRF	26.8	22.4	4.4	16.4179	2
23	987818	68	1	3	1	1	2	2	HRF	14.7	12.5	2.2	14.9659	2
24	981726	59	1	3	2	3	2	2	DLF	56.2	49.3	6.9	12.2775	2
25	990412	81	1	1	5	2	2	1	DRF	82.8	79.6	3.2	3.8647	1
26	990373	57	1	2	1	1	2	2	DLF	28.1	24.6	3.5	12.4555	2
27	984251	65	1	1	3	2	2	2	PLF	25.3	21.9	3.4	13.4387	2
28	979973	69	1	2	4	1	1	1	DRF	34.2	30.6	3.6	10.5263	2
29	969511	56	1	1	2	1	2	2	PRF	22.3	19.8	2.5	11.2107	2
30	980734	69	1	2	1	3	1	1	DLF	30.4	24.7	5.7	18.75	2
31	984223	42	1	2	1	2	2	2	DLF	12.8	10.7	2.1	16.4062	2
32	959661	40	1	3	2	1	2	2	PLF	36.8	32.4	4.4	11.9565	2

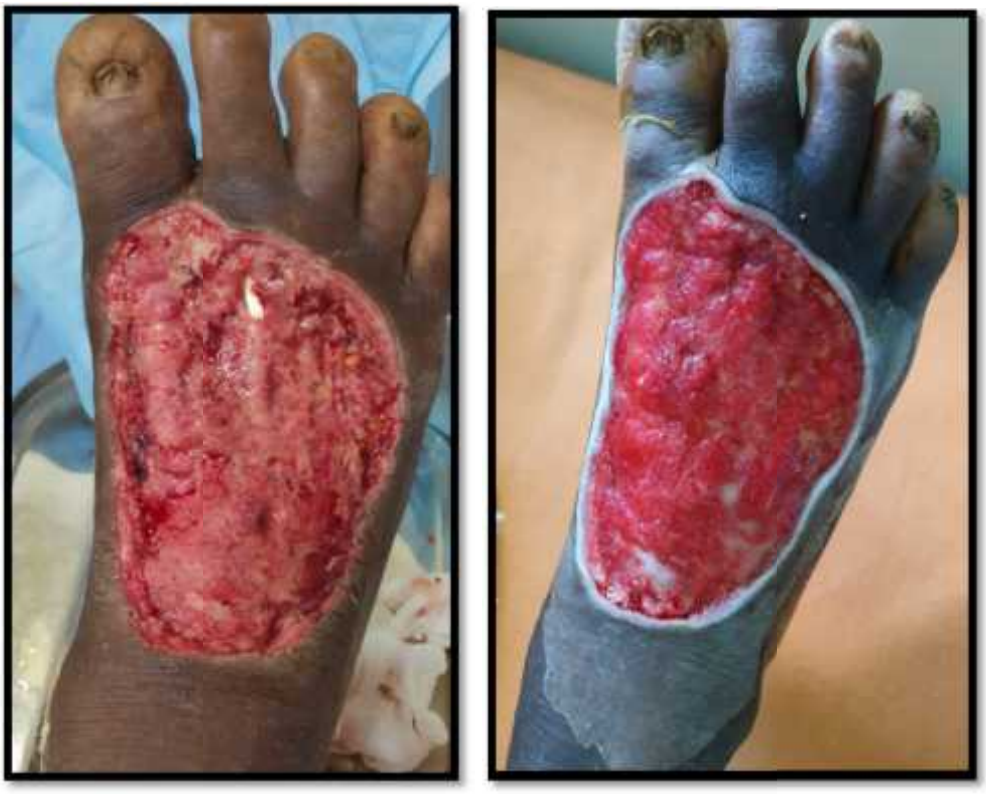


PHOTOGRAPH-1: DRESSING EQUIPMENT



PHOTOGRAPH-2: PHENYTOIN AMPULE

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



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