"A RANDOMISED CONTROLLED TRIAL TO COMPARE PAPAIN-UREA BASED PREPARATION VS SUPEROXIDISED SOLUTION IN THE MANAGEMENT OF GRADE 2-DIABETIC FOOT ULCER"

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ENDORSEMENT

This is to certify that the dissertation entitled **"A RANDOMISED CONTROLLED TRIAL TO COMPARE PAPAIN-UREA BASED PREPARATION VS SUPEROXIDISED SOLUTION IN THE MANAGEMENT OF GRADE 2-DIABETIC FOOT ULCER"** is a bonafide research work done by **CANDIDATE REG NO. BH0114002**.

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LIST OF ABBREVIATIONS USED

AP	-	Antero posterior
ATPase	-	Adenine triphosphatase
BC	-	Before Christ
BMI	-	Body mass index
CI	-	Confidence interval
CSWD	-	Conservative sharp wound debridement
DFU	-	Diabetic foot ulcer
DM	-	Diabetes mellitus
E	-	Eosionophils
E. coli	-	*Escherachiae coli*
e.g.	-	For example
FAC	-	Free available chlorine
g	-	Gram
GDM	-	Gestational Diabetes mellitus
HbA_1C	-	Glycosyated hemoglobin
HDL	-	High density lipoprotein
IDF	-	International Diabetes Federation
IFG	-	Impaired fasting glucose
IGT	-	Impaired glucose tolerance
IP/OPD No	-	In Patients / out patient number
kg	-	Kilogram
L	-	Lymphocytes
Lat.	-	Lateral
LDL	-	Low density lipoprotein

M	-	Monocytes
mg/dL	-	Milligram per deciliter
MIST	-	Minimally invasive surgery training
mm Hg	-	Millimeters of mercury
mmol/L	-	Millimole per litre
mOsm/kg	-	milliosmole per kilogram
MRI	-	Magentic resonance imaging
MRSA	-	Methicillin resistant staphylococcus aureus
N	-	Neutrophil
n	-	Total number
NTR	-	Necrotic tissue removal
OHA	-	Oral hypoglycaemic agent
OR	-	Odds ratio
p	-	Probability valure
PI	-	Povididine iodine
PMN	-	Polymorphonuclear
ppm	-	parts per million
PVD	-	Peripheral vascular disease
RCT	-	Randomized controlled trial
SD	-	Standard deviation
SOS	-	Super-oxidized solution
sq. cms.	-	Square centimeters
USA	-	United States of America
viz.	-	Namely
VRE	-	*Vancomycin-resistant enterococci*

vs.	-	Versus
WHO	-	World Health Organization
wks	-	Weeks
W-S	-	White slough

ABSTRACT

Background and objectives

Enzymatic ulcer debridement is effective in chronic nonhealing ulcers and it decrease exudates, bacterial burden and promote ulcer healing. This study was aimed to compare the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of grade 2 diabetic foot ulcers, as assessed by the appearance of granulation tissue on the end of day 21.

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 2015 to December 2015. A total of 60 Diabetic Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers were enrolled. These patients were divided into two groups of 30 each that is First group (Group A) with superoxidised solution and Second group (Group B) with papain-urea based preparation.

Results

In the present study 80% of the patients in group A and 86% of the patients in group B were males. (p=0.488) The mean age in group A was 61.56 ± 13.00 years compared to 58.53 ± 11.40 years (p=0.341). It was observed that, majority of the patients in group A (70%) and group B (76.67%) has type 2 diabetes mellitus (p=0.559). The mean duration of diabetes in group A was 7.97± 5.65 years compared to 7.00 ± 4.18 years in group B (p=0.453). On day 21 significantly higher number of patients (73.33%) in group B had granulation

compared to group A (46.67%) (p=0.035). It was observed that, wound area before dressing, on day five and day 10 was comparable. Even the reduction in wound area from day 21 to beginning of dressing was also comparable (p> 0.050).

Conclusion and interpretation

Papain-urea seems to be a better enzymatic debriding agent promotes faster granulation compared to superoxidised solution.

Keywords

Diabetic foot ulcer; Debridement; Papain Urea; Superoxidised solution;

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

Worldwide, the frequency of type 2 diabetes is increasing in every country. In 2014, diabetes caused 4.9 million deaths and death is noted in a person every seven seconds. Based on the estimates from International Diabetes Association, worldwide 387 million people have diabetes. This number is expected to rise to 582 million by 2035. A vast majority of these (77%) people live in low and middle income countries.[1]

Diabetes is potential epidemic in India with more than 62 million diabetic individuals.[2,3] It is predicted that, by 2030, it may afflict upto 79.4 million individuals. Other countries like China (42.3 million) and the United States (30.3 million) are also expected to see increase in the number of patients affected by DM.[4,5] India currently faces an uncertain future in relation to the potential burden that diabetes may impose upon the country.[6]

Diabetes mellitus is a chronic and disabling disease which has reached an epidemic proportion in many parts of the world. It is a major and growing concern to global public health. Diabetes results in long term damage, dysfunction of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[1]

The metabolic deregulation due to DM causes secondary pathophysiological changes in various organ systems which impose tremendous burden on the individual and on the health care system. Many complications are associated with DM. These complications arise mainly due to the disruption of the vascular system resulting in inadequate circulation to the peripheral body placing the foot at higher

risk of ulceration and infection. Every chronic disease brings with it fears, concerns, and people with Diabetes are no exception with daunting possibility for infections that never heal, potentially ending in the loss of the affected part of limb.[9] One-third of all diabetic patients have significant peripheral neuropathy and/or peripheral vascular disease (PVD).[8,9]

Diabetic foot problems are the common causes for hospitalization of diabetic patients (nearly 30% of admissions) with 20% of the total health-care costs which is more than all other diabetic complication.[8,9] In India prevalence of foot ulcers in diabetic patients in clinic population is 3%. The prevalence of PVD increases with advancing age to as high as 55% in those above 80 years of age compared to as low as 3.2% below 50 years of age.[10] Also it increases with duration of diabetes that is, 15% at duration of 10 years and 45% after the duration of 20 years.[11]

The management of diabetic foot ulcers needs a multidisciplinary approach. One of the major causes of non-healing of ulcer in diabetes is infection resulting in often hospitalization. The infections are caused by a variety of micro-organism they invade the wound by multiplying. Furthermore they produce harmful toxic substances which destruct the tissue and disturb wound healing.[12]

The successful management of diabetic foot ulcers prompts offloading the wound by using appropriate therapeutic footwear,[13] daily saline or similar dressings so as to provide a moist wound environment, debridement, antibiotic therapy (if osteomyelitis or cellulitis is present),[14] optimal diabetic control, and evaluation and correction of peripheral arterial insufficiency.

Various factors affecting wound healing are host related factors or endogenous factors. Healing is rapid in children and young persons and delayed in debilitated or malnourished having anemia and hypoproteinaemia. Obesity also has an adverse effect on wound healing. Uncontrolled diabetes results in reduced inflammation, angiogenesis and collagen synthesis. Jaundice and uraemia adversely affect wound healing. Wasting caused by chronic illness leads to poor wound healing. Malignancy is natural to cause poor wound healing. Patients on cytotoxic agents, chronic steroids intake and those having autoimmune deficiencies are more prone to wound infection and delayed healing. Exogenous factors include duration of surgery, glove punctures, emergency procedures, air borne contamination, wound contamination, tissue perfusion, microbes causing infection.[15]

Tissue level factors or local factors like poor blood supply, inadequate oxygenation undue tension in suturing, tissue necrosis and local infection have profoundly deleterious effect on all aspects of wound healing.[15]

Although a multimodel therapy is the basis of wound healing, an ideal antiseptic is one that is rapidly lethal to all forms of bacteria and their spores, capable of bactericidal activity for a prolonged period, has no injurious effect on wound healing tissues.

There has always been a search for an ideal antiseptic that is rapidly lethal to all forms of bacteria and their spores, capable of bactericidal property for a prolonged period with no ill effect on host tissues. Superoxidized solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds. Superoxidized Solutions have shown to be both safe and efficient

as a wound care product that moistens, lubricates, debrides and reduces the microbial load of various types of lesions.[16,17] Super oxidized solutions are elelctrochemically processed aquous solutions manufactured from pure solutions which is rich in reactive oxygen species with neutral pH and longer half life (>12 months). SOS is a stable, non-flammable and non-corrosive bactericidal, virucidal, fungicidal and sporocidal solution that is ready to use with no further dilution or mixing.

Debridement involves removal of dead, damaged, or infected tissue, which improves the healing potential of the remaining healthy tissues. Depending on the wound tissue type, different debridement techniques are recommended:[18,19] Many modalities of debridement are now available as surgical/sharp, mechanical, autolytic, enzymatic and biologic with major emphasis on enzymatic wound debridement. Enzymatic wound debridement has proven efficacy in management of ulcers. It uses topical enzymes to remove necrotic tissue by digesting and dissolving the devitalised tissue in the ulcer-wound bed.[20,21]

It is postulated that, enzymatic ulcer debridement is effective in debridement of chronic nonhealing ulcers and also decrease exudates, bacterial burden and promote ulcer healing.

A well-known and widely used enzymatic system is the papain-urea combination. In this system, papain is used to attack and breakdown any protein contaning cysteine residues. The combination of papain and urea is probably twice as effective in protein digestion as papain alone. An advantage of the papain urea

combination may be nonspecific bulk debridement within a broad pH range 3.0–12.0.[22]

Super oxidized solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds. Super oxidized Solutions have shown to be both safe and efficient as a wound care product that moistens, lubricates, debride and reduces the microbial load of various types of lesions.[23,24] As we compare both, papainurea combination is used to attack and break down any protein containing cysteine residues. This property of papain renders the combination quite nonselective because most proteins, including growth factors, contain cysteine residues. As, superoxidised contains no cysteine residues. An advantage of the papainurea combination may be nonspecific bulk debridement within a broad pH range (3.0-12.0), whereas super oxidized solutions are elelctrochemically processed aquous solutions manufactured from pure solutions which is rich in reactive oxygen species with neutral pH. The benefits of urea are its strong osmotic power which facilitates hydration of the wound.[25]

However there is limited data on the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of diabetic foot ulcers. Considering the burden of diabetic foot ulcer and limited data on the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of diabetic foot ulcers the present study was undertaken to compare the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of grade 2 diabetic foot ulcers, as assessed by the appearance of granulation tissue on the end of day 21.

OBJECTIVES

The objectives of this study were to compare the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of grade 2 diabetic foot ulcers, as assessed by the appearance of granulation tissue on the end of day 21.

REVIEW OF LITERATURE

DIABETES MELLITUS

Diabetes mellitus (DM), a chronic metabolic disorder of impaired metabolism of carbohydrates, fats, and proteins, characterised by hyperglycaemia resulting from decreased utilisation of carbohydrate and gluconeogenesis from amino acids and fatty acids.[26]

First diseases described with an Egyptian manuscript mentioning “too great emptying of urine”.[27,28] Indian physicians around same time identified the disease and classified it as “Madhumeha” or “Honey urine”, noting urine would attract ants. “Diabetes” or “to pass through” was first used in 230 BC by Greek Apollonius of Memphis. Galen named the disease “diarrhoea of the urine” (diarrhoea urinosa).[29]

Classification

Diabetes is classified into four broad categories viz. type 1, type 2, gestational diabetes and other specific types. The "other specific types" are a collection of few dozen individual causes.[30]

Type 1 DM is characterized by loss of insulin producing beta cells of the islets of langerhans in pancreas, leading to insulin deficiency. Majority of type 1 diabetes is the immune-mediated nature, in which T-cell mediated autoimmune attack leads to the loss of beta cells and thus insulin. Traditionally, termed as juvenile diabetes because a majority of these diabetes cases were in children.[30]

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. In early stages of type 2, the predominant abnormality reduced insulin sensitivity. At this stage, hyperglycaemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. Type 2 DM is due to genetics and lifestyle factors including obesity, lack of physical activity, poor diet, stress and urbanization. A lack of exercise is believed to cause 7% of cases.[30]

Gestational DM (GDM) involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery.[30]

Prevalence

Worldwide

Prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. There are 382 million people living with diabetes worldwide. Worldwide prevalence of diabetes in adults (aged 20-79 years) was estimated to be 135,285 million in 1995 and 2010 respectively and is expected 300 million in 2025 and 439 million in 2030. Statistics showed significant increase (155 million) of diabetes in adults from 1995 to 2010. By 2035,592 million people or 1 in 10 people will have diabetes and 316 million people are currently at high risk of developing type 2 diabetes, with the number expected to increase to almost 500 million within a generation.[6,30-36]

According to the International Diabetes Federation survey in the year of 2013, nearly 98.4 million people with diabetes (20 - 79 years) live in China, is the

top most country and India is the second i.e., nearly 65.1 million. Table 1 presents survey of the year 2013 on diabetes affected top 10 countries and their number of diabetic people at age group of 20-79.[6,30-35]

Top ten countries with diabetes and number of people with age 20–79 years[37]

Serial number	Country / territory	Number (Million)
1.	China	98.40
2	Indian	65.10
3	United states of America	24.40
4	Brazil	11.90
5	Russian federation	10.90
6	Mexico	8.70
7	Indonesia	8.50
8	Germany	7.60
9	Egypt	7.50
10	Japan	7.20

Geographical distribution

Prevalence of diabetes is higher in developed than in developing countries. By 2025, more than 75% of people with diabetes will reside in developing countries, as compared with 62% in 1995. Europe has the highest prevalence of type 1 diabetes in children but in South-East Asia, almost half of people with diabetes are undiagnosed. 11% of people with diabetes live in Middle East and North Africa where as it was 6% in Africa but in Africa, 76% of deaths due to diabetes are in

people under the age of 60. North America and Caribbean spent more on healthcare for diabetes than in any other region.[6,30-35]

Sex predilection

Prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. [6,30-35]

Indian scenario

According to The International Diabetes Federation (IDF) estimation India will have rise in people living with diabetes up to 87.0 million by 2030 from 50.8 million (2010), making it the 'Diabetes Capital' of the world.[38-40]

This prevalence is increasing not only in urban but also in rural area. According to the World Health Organization (WHO) criteria, the prevalence of known diabetes was 5.6% and 2.7% among urban and rural areas, respectively.[41]

Recently, in Karnataka, Rao CR. et al.[42] reported overall prevalence of diabetes as 16%. Increasing age showed two-fold, four-fold, and six-fold higher odds for 40 – 49, 50 – 59, and ≥ 60 years age group, respectively, as compared to the 30 - 39 year age group ($p< 0.001$). 19% of the males had diabetes, (OR = 1.38, 95% confidence interval [CI] = 1.01 – 1.88). In the high socioeconomic strata, 32% of the subjects had diabetes ($P = 0.018$ unadjusted odds ratio 3.29, 95% CI = 1.40 – 7.74).

In India, DM is considered, a disease of grave concern not only because of rapidly increasing prevalence, but also because various studies have shown rising prevalence of diabetes in young and middle aged people. This is mainly due to the economic transition, rapid urbanization and changing lifestyles, tobacco use,

excessive alcohol consumption, and insufficient physical activity which are major risk factors for diabetes mellitus.[43]

Risk factors for Type 2 Diabetes Mellitus[38]

- Family history of diabetes (i.e. parent or sibling with Type 2 diabetes)
- Obesity (body mass index [BMI] ≥25 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g. African, American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)
- History of GDM or delivery of baby > 4kg (>9 Ib)
- Hypertension (blood pressure ≥ 140/90 mm Hg)
- High density lipoprotein (HDL) cholesterol level ≤ 35mg/dL (0.90mmol/L) and / or a triglyceride level ≥ 250mg/dL (2.82 mol/L)
- Polycystic ovary syndrome or acanthosis nigricans.
- History of vascular disease.

Symptoms

Symptoms are similar in both types of diabetes but vary in their intensity. Symptoms develop more rapidly in type 1 diabetes and more typical. Its include frequent urination, extreme thirst and/or hunger, weight loss, fatigue, numbness and increased infections.[38]

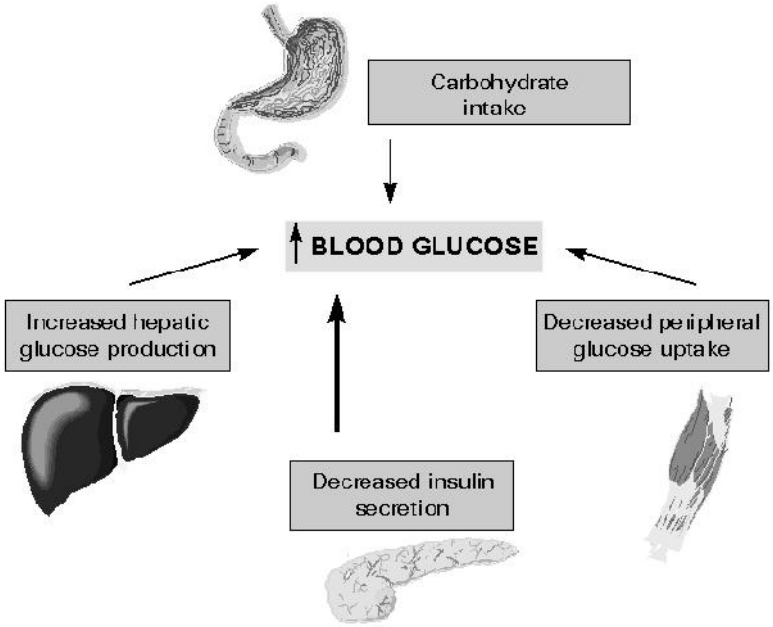


Figure 1. Pathophysiology of type 2 diabetes mellitus[1,43]

Diagnosis

The National Diabetes Data Group and World Health Organization (WHO) have issued diagnostic criteria for DM based on the following premises:[1]

Criteria for the Diagnosis of DM

- Symptoms of diabetes plus random blood glucose concentration 11.1 mmol/L (200 mg/dL)[a] *or*
- Fasting plasma glucose 7.0 mmol/L (126 mg/dL)[b] *or*
- Two-hour plasma glucose 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a]Random is defined as without regard to time since the last meal.
[b]Fasting is defined as no caloric intake for at least 8 h.
[c]The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Complications

Poor control of diabetes can lead to increased risk of heart disease, high blood pressure, stroke, nerve disease, kidney and bladder failure, gum disease, blindness, foot and leg infections, sexual dysfunctions, pregnancy complications. Uncontrolled diabetes can lead to biochemical imbalance that can cause life-threatening events, such as diabetes ketoacidosis and hyperosmolar coma.[30]

Chronic Complications of DM[44-50]

The chronic complications of DM affect many organ systems and those may be responsible for the majority of morbidity and/or mortality associated with the disease.

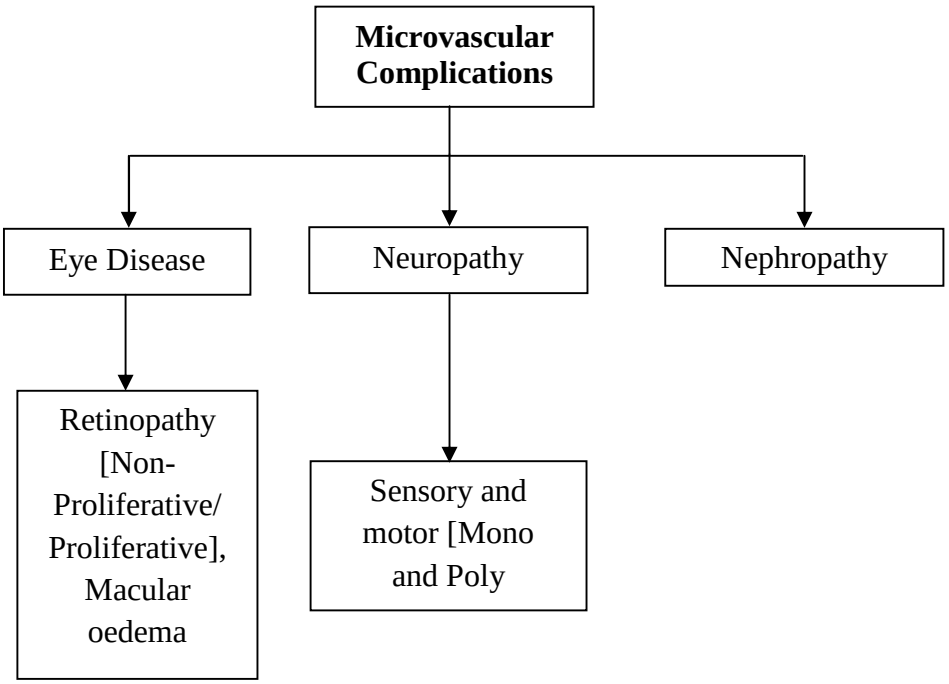


Figure 2. Microvascular complications seen in DM

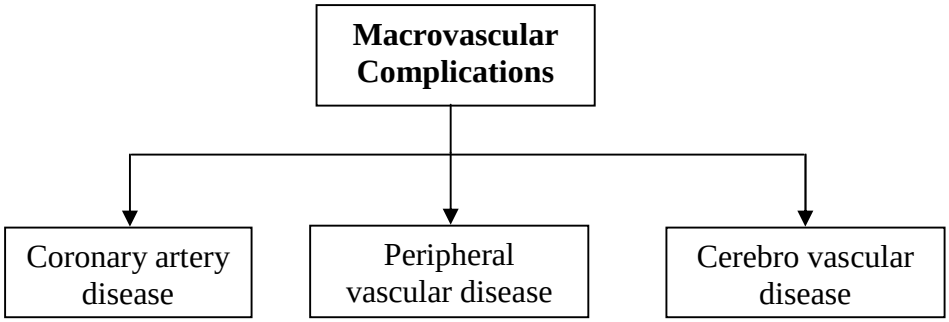


Figure 3. Macrovascular complications seen in DM

Other:[44-50]

- Gastro-intestinal problems [Gastroparesis, diarrhoea]
- Genitor-urinary problems [Uropathy / Sexual dysfunction]
- Dermatologic problems.
- Infections.
- Cataracts and Glaucomas.

Microvascular complications in both type 1 and type 2 diabetes mellitus, results fro chronic hyperglycemia.

Complications in lower extremities and diabetes mellitus:[44-50]

- Foot ulcers and infections are major and important source of morbidity in persons with DM.
- The reasons for the increased incidence of these disorders in DM is because of the interaction of several pathogenic factors:
    - Neuropathies.
    - Peripheral arterial diseases.
    - Abnormal foot biomechanics.

Neuropathy

Neuropathy is present in over 80% of the patients with foot ulcers.

Peripheral sensory neuropathy:

It interferes with normal protective mechanisms and allows patient to sustain major or minor trauma to the foot repeatedly, often without knowledge of the injury to the patient.

Motor and sensory neuropathy:

It generally leads to abnormal foot muscle mechanics and structural changes in the foot [e.g., hammer toe, claw toe deformity, prominent metatarsal heads, Charcot arthropathy].

DIABETIC FOOT ULCER

Diabetic foot ulcer (DFU), the most common complication of DM that usually fail to heal, leading to lower limb amputation. Its a common complication of DM that has shown an increasing trend over previous decades.[51]

A diabetic foot infection is most simply defined as any inframalleolar infection in a person with diabetes mellitus. These include paronychia, cellulitis, myositis, abscesses, necrotizing fascitis, septic arthritis, tendonitis, and osteomyelitis. The most common and classic lesion, however, is infected diabetic “mal perforans” foot ulcer.[52] Wound infection, the deposition and multiplication of bacteria in tissue with colony count of more than 10^5 bacteria per gram of tissue with an associated host reaction.[53]

DFU occur as a result of various factors, such as mechanical changes in conformation of the bony architecture of the foot, peripheral neuropathy, and atherosclerotic peripheral arterial disease.

Anatomy of the foot[38,54]

The human foot acts as a pliable platform to support the body weight in the upright posture and as a lever to propel the body forwards in walking, running or jumping. It has 26 bones, 29 joints, 42 intrinsic muscles, various ligaments, 4 mm thick skin, exquisite nerve supply and abundant vascularity with good collaterals. These component works together to provide the body with support, balance with mobility.

Parts

Structurally the foot has three main parts;

1. *The fore foot:* It is composed of phalanges and metatarsals. They are connected together by metatarso phalangeal joint at the balls of foot. Fore foot bears, half the body weight and balance pressure on the balls of foot.
2. *The mid foot:* It is composed of 5 tarsals bones. It forms the foot's arch and serves as a shock absorber.
3. *The hind foot:* It links the mid foot to ankle. It is composed of 2 long bones of lower leg, the tibia and the fibula which forms ankle joint with talus. This subtalar joint is formed between talus and calcaneum which is cushioned inferiorly by a fat layer.

Arches

The foot consists of 3 arches.

1. Medial longitudinal arch

    - It is the highest and the most important arch of foot.
    - Composed of calcaneum, talus, navicular, cuneiforms and first three metatarsal bones. The submit of the arch is formed by talus.
    - Acts as a shock absorber.

2. Lateral longitudinal arch

    - Characteristically low arch.
    - Composed of calcaneum, cuboid, fourth and fifth metatarsal bones. The submit of the arch is formed by calcaneum.
    - It transmits the body weight and thrust to the ground.

3. Transverse arch

    - It is a continuous structure formed by cuboid, three cuneiforms and the bases of the metatarsal bones.

Functions of the arches of the foot

1. They distribute body weight to the weight bearing areas of the sole mainly heel and the base of the toes (first and fifth).
2. They act as a springs chiefly the medial longitudinal arch which helps in walking and running.
3. They also act as a shock absorbers in stepping and jumping.

4. The concavity of the arches protects the soft tissue of the sole against pressure.

Sole

The skin of sole is about 4 mm thick, is adapted for weight bearing. There are subcutaneous concentrations of fat over the weight bearing areas such as heel, lateral margin of sole and across plantar aspect of metatarsal heads. Numerous fibrous bands between the skin and plantar aponeurosis prevent undue movement of sole during walking.

Muscles

Intrinsic

- Origin and insertion are located within the foot.
- It includes plantar flexors, dorsiflexors, abductors and adductors of toes.
- Also support the arches of foot.

Extrinsic

- Origin of these muscles are in the lower leg.
- They have long tendon that crosses the ankle to insert on bones of foot except talus.
- They are responsible for the movement at ankle, foot and toes.
- They also support the arches of foot.

  Major joints and movements

  - Ankle joint – Dorsiflexion and plantar flexion.

- Subtalar joint – Inversion and eversion.
- Midtarsal joint – Abduction and adduction.

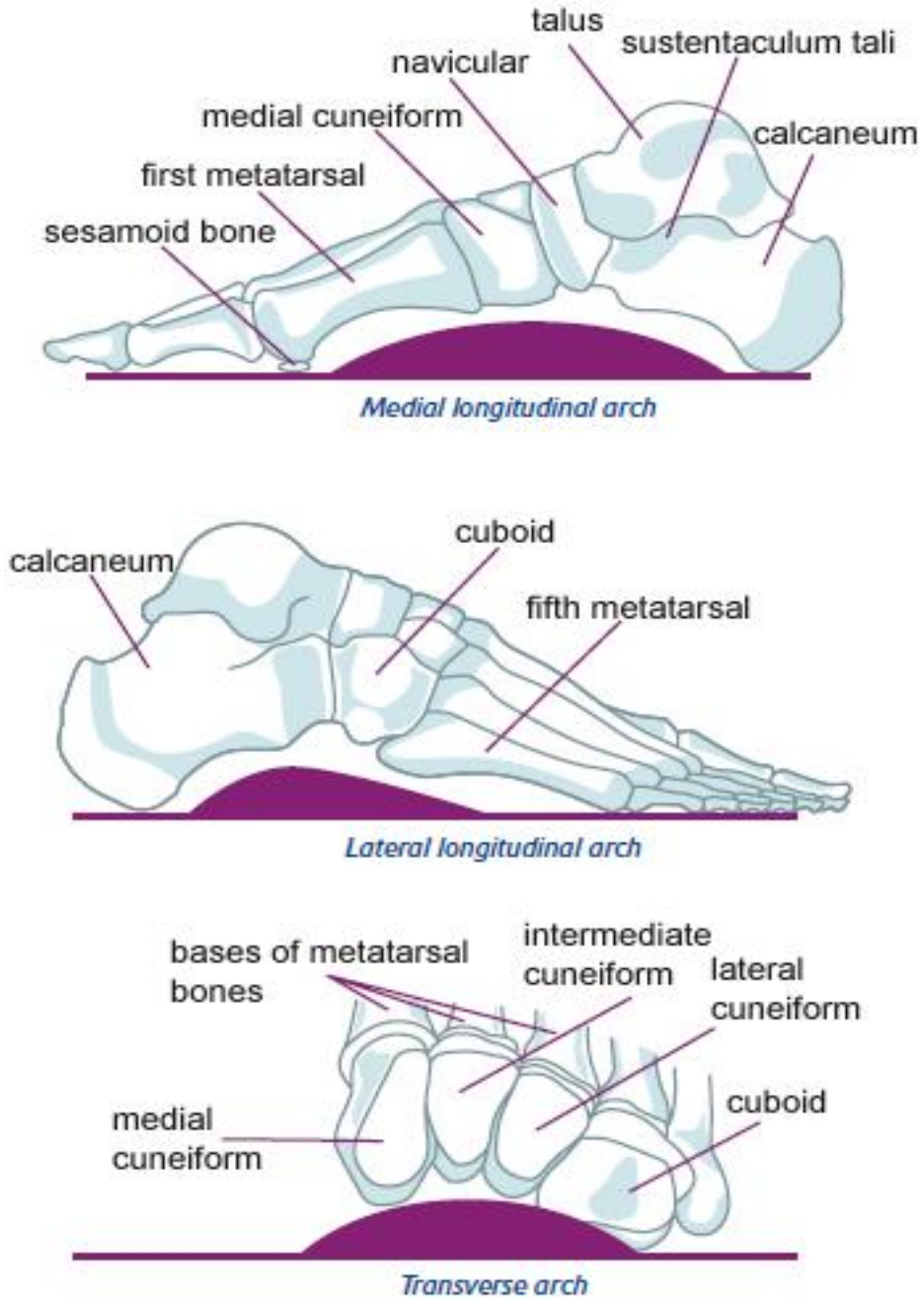


Figure 4. Arches of the foot[55,56]

Blood supply

Anterior tibial artery continues as a dorsalis pedis artery in the foot. Dorsalis pedis artery gives off arcuate artery that along with its branches supplies the outer four toes. Dorsalis pedis artery continues down to supply great toe. Posterior tibial artery in the sole of foot divides into two branches, the lateral and medial plantar arteries that supplies the sole of foot. The peroneal artery descends down and supply posterior and the outer aspect of heel.

Nerve supply

Sensory nerve supply

Dorsum

- Saphenous nerve: It supplies the medial border of the foot upto the ball of the great toe.
- Superficial peroneal nerve: It supplies entire dorsum of the foot except lateral border, medial border and the cleft between first and second toe.
- Sural nerve: It supplies the lateral border of foot upto the tip of little toe.
- Deep peroneal nerve: It supplies the cleft between the first and second toes.
- Digital branch of the medial and lateral plantar nerve supplies the distal part of the dorsum of toes.

Sole

- Medial calcaneum branch of tibial nerve: It supplies posterior and medial portion of sole.

- Medial plantar nerve: It supplies the anteromedial portion of sole and medial three and half digits.
- Lateral plantar nerve: It supplies anterolateral portion of the sole and lateral one and half digits.

Motor nerve supply

- Deep peroneal nerve.
- Superficial peroneal nerve.
- Tibial nerve - Medial plantar nerve; Lateral plantar nerve.

Epidemiology

Approximately 15% of all patients with diabetes will develop a peripheral ulcer. 20% of all patients with diabetes admitted to a hospital will have a skin ulcer. The risk of amputation in a patient with diabetes is 15–40 times higher than in a patient without diabetes. The presence of an ulcer in a diabetic patient has a deep impact on the quality of life for the patient and on the delivery of care. The cost of care for diabetic ulcers and the associated amputations is staggering. Although the prevalence of chronic ulcers has been estimated to be 120/100,000 people between 45–64 year of age, the prevalence increases to more than 800/100,000 people over the age of 75 year. Persons with diabetes have up to a 40-fold greater risk of lower extremity amputation than their non-diabetic counterparts. There were approximately 86,000 hospital discharges for diabetes-related non-traumatic amputations in the United States in 1996. The 5-year survival rate after amputation of a diabetic limb is less than 50%. These grim statistics reflect an increased prevalence of peripheral lesions in diabetes, but also delayed healing.[44,57]

Risk factors

Recent studies have indicated multiple risk factors associated with the development of DFU. These risk factors are as follows: gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index, and other comorbidities such as retinopathy, diabetic peripheral neuropathy, peripheral vascular disease, glycated hemoglobin level (HbA_1C), foot deformity, high plantar pressure, infections, and inappropriate foot self-care habits.[51]

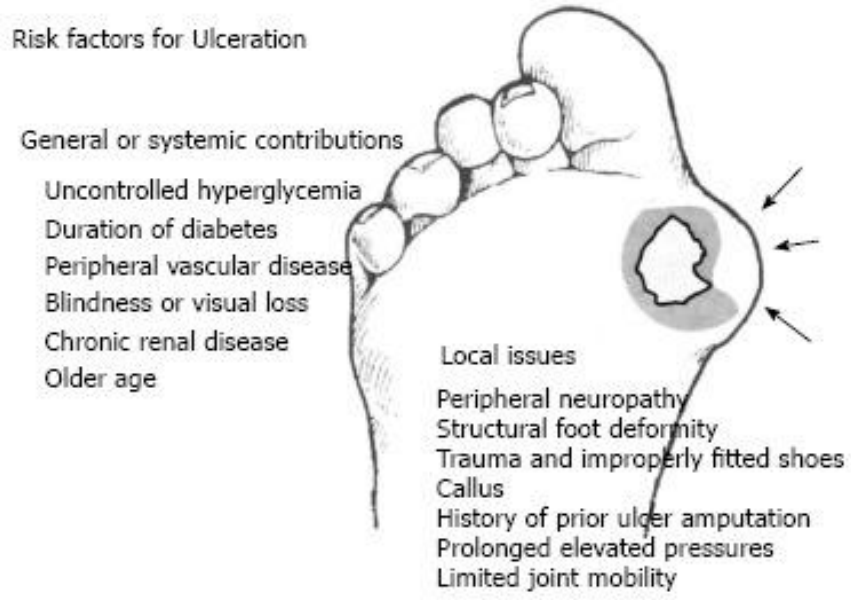


Figure 5. The risk factors for diabetic foot ulcer[58]

Although the literature has identified a number of diabetes related risk factors that contribute to lower-extremity ulceration and amputation, to date most DFU has been caused by ischemic, neuropathic or combined neuroischemic abnormalities. Pure ischemic ulcers probably represent only 10% of DFU and 90% are caused by neuropathy, alone or with ischemia. [51]

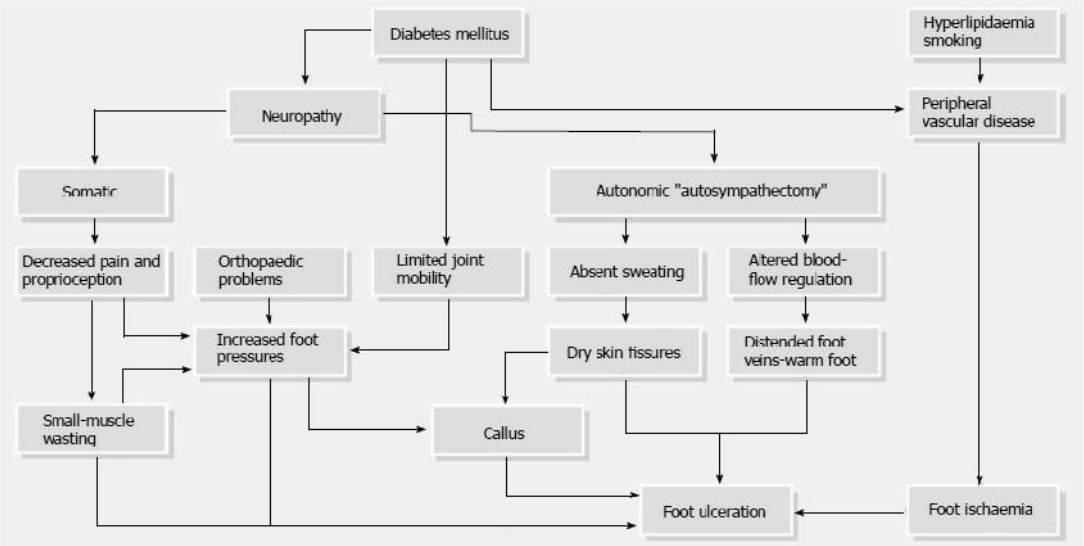


Figure 6. Etiology of diabetic foot ulcer[59]

In total, the most common pathway to develop foot problems in patients with diabetes is peripheral sensori-motor and autonomic neuropathy that leads to high foot pressure, foot deformities, and gait instability, which increases the risks of developing ulcers.[59]

Pathophysiology

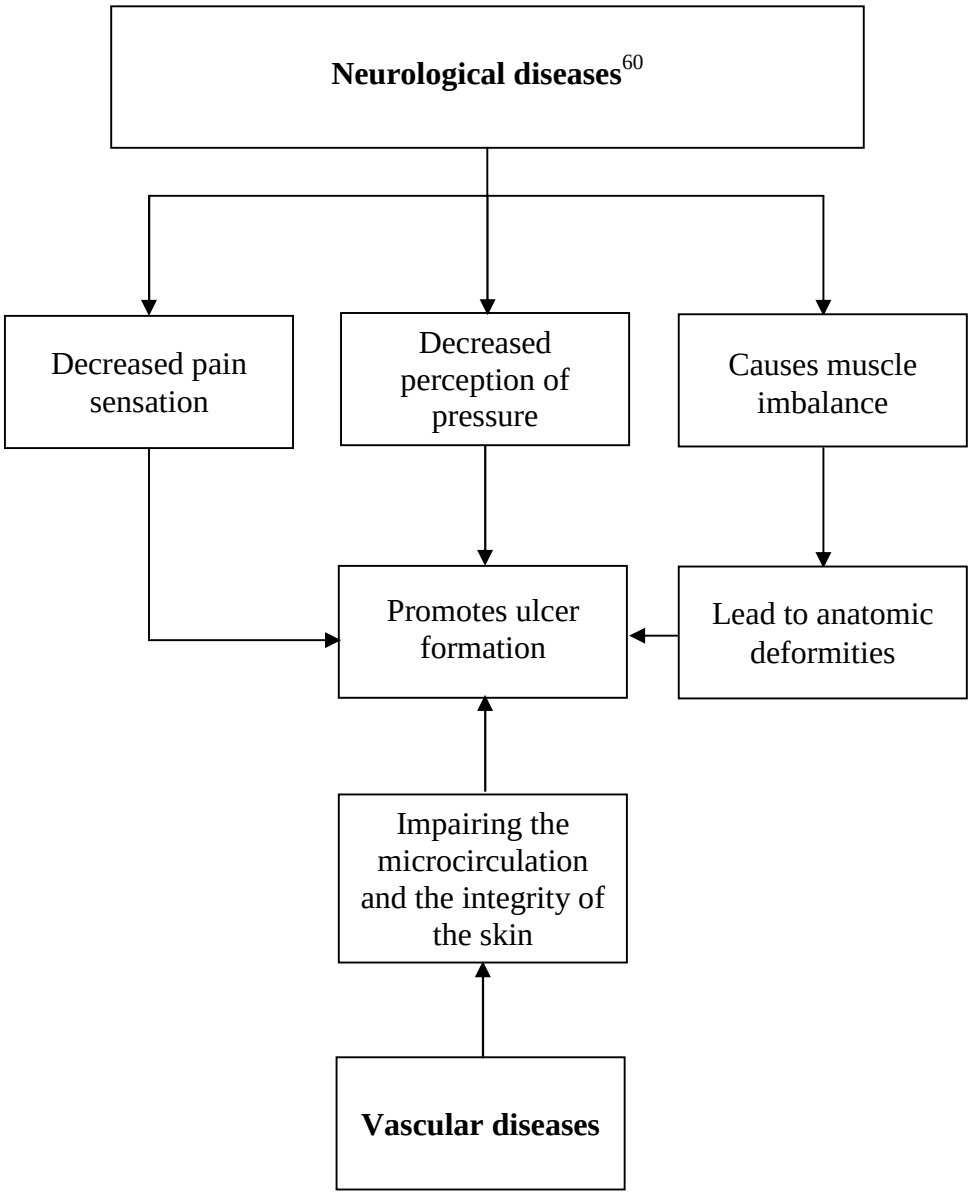


Figure 7. Pathogenesis of Diabetic Foot

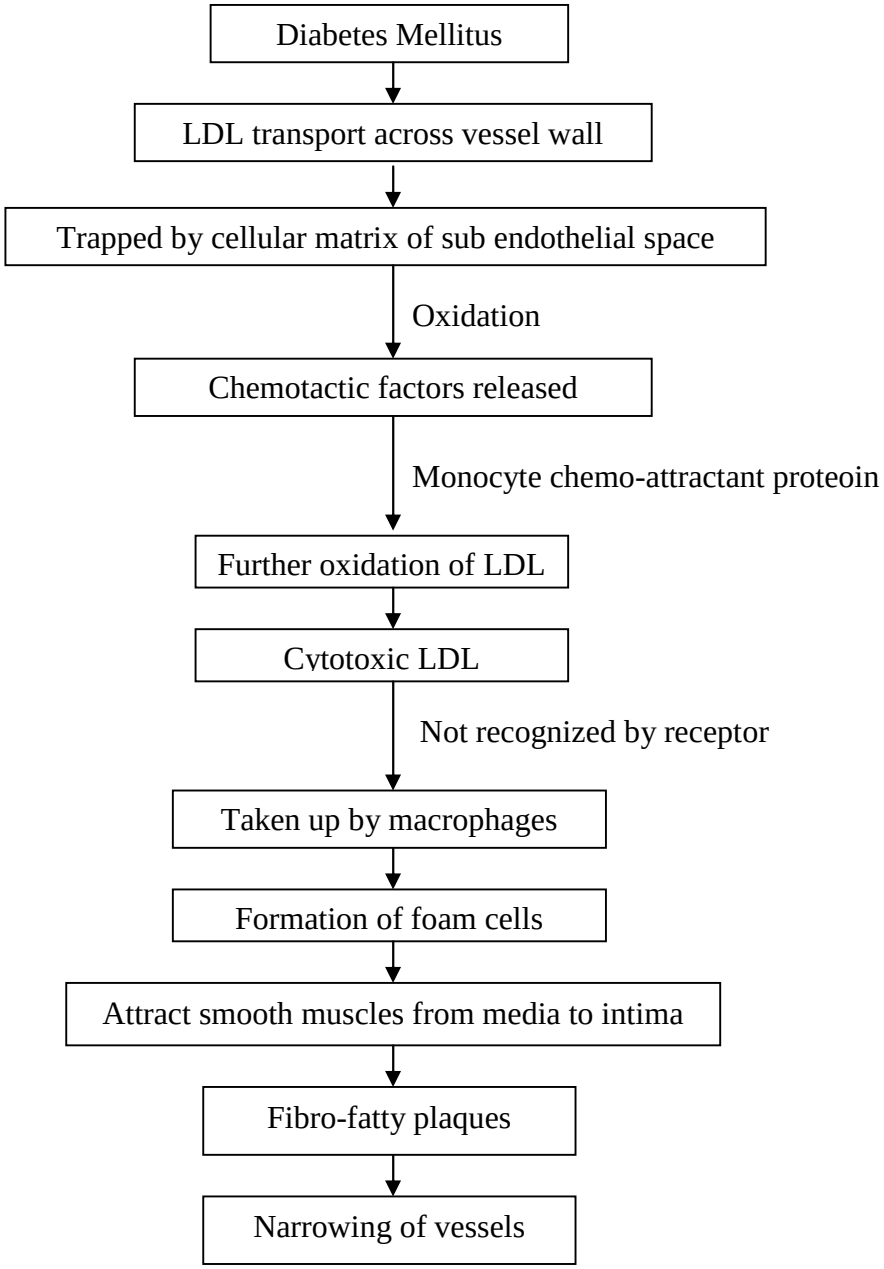


Figure 8. Pathophysiology of diabetic vasculopathy

Atherosclerosis and peripheral neuropathy occur with increased frequency in persons with DM. Development of atherosclerosis is accelerated in DM leading to increased morbidity and mortality. All the large vessels are involved in this process and clinical manifestations are apparent as a result of atherosclerotic narrowing and thrombosis of coronary, cerebral and leg vessels.

The pathophysiology of diabetic peripheral neuropathy is multifactorial and is due to vascular disease occluding the vasa nervorum; endothelial dysfunction; deficiency of myoinositol-altering myelin synthesis and diminishing sodium-potassium adenine triphosphatase (ATPase) activity; chronic hyperosmolarity, causing edema of nerve trunks; and effects of increased sorbitol and fructose.[61]

The result of loss of sensation in the foot is repetitive stress; unnoticed injuries and fractures; structural foot deformity, such as hammertoes, bunions, metatarsal deformities, or Charcot foot. Unnoticed excessive heat or cold, pressure from an ill- fitting shoe, or damage from a blunt or sharp object accidentally left in the shoe may cause blistering and ulceration.

Microbiologic features of diabetic foot

Aerobic Gram-positive cocci are the predominant bacteria that colonize and acutely infect breaks in the skin. *Staph aureus* and the hemolytic streptococci (groups A, C, and G, but especially group B) are the most commonly isolated pathogens.[62] Chronic wounds develop a more complex colonizing flora, including enterococci various Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa*, and nonfermentative Gram-negative rods.[63] Hospitalization, surgical procedures, and, especially, prolonged or broad-spectrum antibiotic therapy may predispose patients to colonization and/or infection with antibiotic-resistant organisms (*MRSA* or *vancomycin-resistant enterococci* [VRE]).[64]

Pathogens associated with various clinical foot-infection syndromes[65]

Foot- infection syndrome	Pathogens
Cellulitis without an open skin wound.	*Beta-hemolytic streptococcus** and *Staph aureus*
Infected ulcer and antibiotic naïve (X).	*Staph aureus* and *beta-hemolytic streptococcus**
Infected ulcer that is chronic or was previously treated with antibiotic therapy (Y).	*Staph aureus, beta-hemolytic streptococcus*, and *Enterobacteriaceae*
Ulcer that is macerated because of soaking (Y).	*Pseudomonas aeruginosa* (often in combination with other organisms)
Long-duration nonhealing wounds with (Y, Z) prolonged broad-spectrum antibiotic therapy	Aerobic gram-positive cocci (*Staph aureus, coagulase-negative staphylococci, and enterococci*), *diphtheroids, Enterobacteriaceae, Pseudomonas species, nonfermentative gram-negative rods, and, possibly, fungi*
"Fetid foot": extensive necrosis or gangrene or malodorous (Z)	Mixed aerobic gram-positive cocci, including *enterococci, gangrene, malodorous Enterobacteriaceae, nonfermentative gram-negative rods,* and *obligate anaerobes*

*Groups A, B, C, and G; X Often monomicrobial; Y Usually polymicrobial; Z Antibiotic-resistant species (eg, *MRSA, vancomycin-resistant enterococci*, or *extended-spectrum beta-lactamase–producing gram-negative rods*) are common.

Evaluation

- Characteristics: Size, depth, appearance, discharge and location.
- Etiological assessment: Neuropathic, ischemic, or neuro-ischemic.
- Screening for neuropathy.
    - Pressure of a 5.07 (10-g) Semmes Weinstein monofilament.

  - Vibration sensation with the use of standard tuning fork (128 cycles per second)
  - Neurologic reflex hammer.
- Probing of ulcer for underlying osteomyelitis.
- Culture sensitivity of the discharge.
- Radiograph for underlying osteomyelitis.
- Colour Doppler study for vascular pathology.
- MRI for Charcots neuropathy.

Wound care management

Physiology of wound healing

When the skin is wounded, a complex series of cellular and chemical events are initiated which act on the damaged tissues – blood vessels, dermis, and epidermis. Wounds that results in limited tissue loss, such as surgical wounds, have a tendency to heal rapidly on the surface as opposing edges of the wound are in close proximity for cellular and structural repair. The wound is healed in about a week, but will continue to mature for a year or more. During this time the structural architecture of the wound changes, the scar usually flattens, and the skin regains most of its pre-wound tensile strength.[66]

In wounds where significant tissue loss occurs the damaged edges are usually unsuitable for primary closure. In this case, the tissue defect must be made up before the wound can heal. To facilitate healing, dressings are applied to try to protect the wound from contamination and keep the wound surface moist to maintain the integrity of the cells present in the defect. In a dry wound environment, dividing

cells at the wound edges are unable to migrate into those areas occupied by dry scab material.[66]

Wound healing process

The biological mechanism associated with wound healing is complex and still not well understood. Although there is much to learn about the detail of the processes involved, some of the general concepts of healing are understood.[67]

Chronic open wounds, such as leg ulcers and pressure sores, heal by secondary intention or granulation, rather than primary intention (the means by which a surgical incision heals). Platelet aggregation during haemostasis liberates a number of soluble mediators, including platelet-derived growth factor, which initiate the healing process.[67]

Haemostasis is followed by an early inflammatory phase that is characterised by vasodilatation, increased capillary permeability, complement activation and polymorphonuclear (PMN) and macrophage migration into the wound.[67]

Polymorphonuclears predominate during the first days of post wound occurrence, with the macrophage becoming the predominant inflammatory cell within 3 days. Macrophages are large, mobile and actively phagocytic, engulfing bacteria and devitalized tissue and acting effectively as the body's own debridement system. Additionally, macrophages are considered to play a key role in regulating subsequent events in the healing process. This is achieved by secretion of a number of factors that regulate their own and other cell functions. These factors are responsible for the chemotactic attraction of more macrophages and the migration and induction of proliferation by fibroblasts and endothelial cells. The increasing

number of fibroblasts and endothelial cells forming granulation tissue around the fifth day post-injury heralds the 'proliferative phase'.[67]

Fibroblasts are the 'factory cells' of the wound healing module. They are rich in mitochondria, endoplasmic reticulum, and Golgi apparatus essential for protein synthesis. Fibroblasts synthesize collagen and ground substance (proteoglycans and fibronectin), which support new cells, and the fragile capillary buds, which appear around this time (angiogenesis). The endothelial buds become canalised, and are thus able to increase the vascularity and hence oxygen tension of the new tissue, so responding to the large metabolic demand of tissue repair. Epithelialisation requires the migration of epithelial cells across the granulation tissue, to close the epidermal defect.[67]

Collagen synthesis continues for many months after wound closure, but also undergoes continous lysis, so a delicate balance exists between the two processes. This final remodelling phase, accompanied by increasing tensile strength of the wound, and a decreasing cellularity, may continue for up to a year.[67]

The healing process is considered to be regulated by cytokines and growth factors, and recent studies have demonstrated that the cytokine environment in a healing chronic wound is different from that in a non-healing wound.[68] However, the precise nature of the defect(s) leading to non-healing remain to be defined.

Wound

It is a breach in the normal tissue continuation resulting in a variety of cellular and molecular sequelae.

Wound healing

Healing - Replacement of destroyed tissue by living tissue.

Stages of Wound Healing[34]

1. Stage of Inflammation
2. Wound Contraction
3. Epithelialization
4. Granulation tissue formation
5. Scar Remodeling.

Stage of Inflammation: (4-6 days)

Inflammation begins immediately after disruption of tissue integrity. Platelets become adherent & with clotting factors form haemostatic plug to stop bleeding from the small vessels. Transient vasoconstriction followed by vasodilatation

Histamine-Primary mediator of inflammatory vascular response, liberated by platelets, mast cells & granulocytes. It produces local vasodilatation and increases permeability of small blood vessels. WBC's migrate into wounds & start engulfing& removing cellular debris & injured tissue fragments. Monocytes are dominant cell type by 5^{th} day.

Wound Contraction

Begins on 4thday, completes by 14th day, and causes reduction in size of wound.

Epithelialization

Epidermis immediately adjacent to wound edge begins thickening on the first day. Occurs by proliferation and migration of the marginal basal cells lying close to wound margin. Fixed basal cells in the zone near the wound edge proliferates & daughter cells migrate.

Granulation tissue formation

Mainly formed by proliferation and migration of the surrounding connective tissue elements. Composed of capillary loops and fibroblasts with a variable number of inflammatory cells. Highly vascular tissue which turns into an avascular scar tissue Stage of Vascularization: Ingrowth of capillary loops and fibroblasts which form living granulation tissue known as organization. Stage of Devascularization: Fibroplasia proceeds and vessels undergo atrophy, lumens obliterated due to intimal proliferation, so granulation tissue looks pale

Scar Remodelling

Collagen synthesis

Tensile strength gain begins from 5^{th} day and increases rapidly up to 17^{th} day and slows down.

Stages of Wound Healing

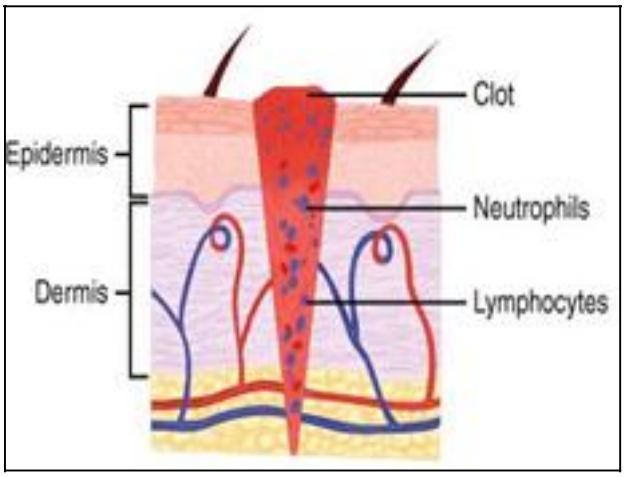


Figure 9 : Inflammatory phase-infiltration by mononuclear cells & lymphocytes

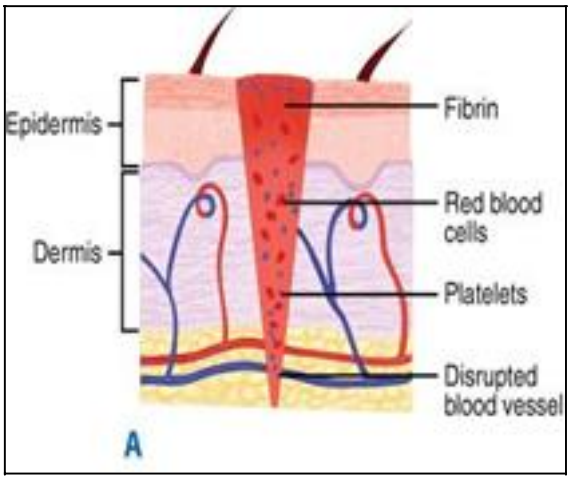


Figure 10: Inflammatory phase

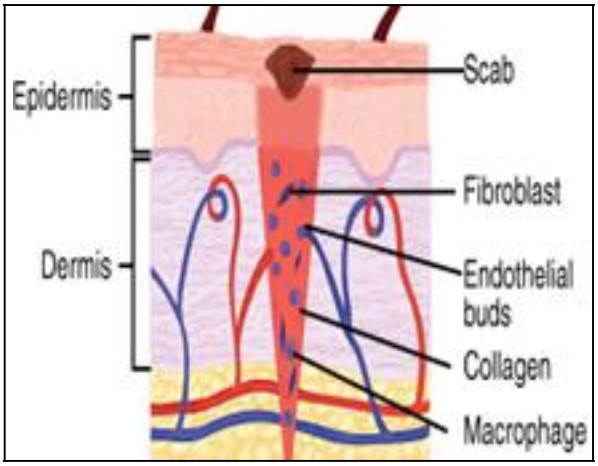


Figure 11. Proliferative phase

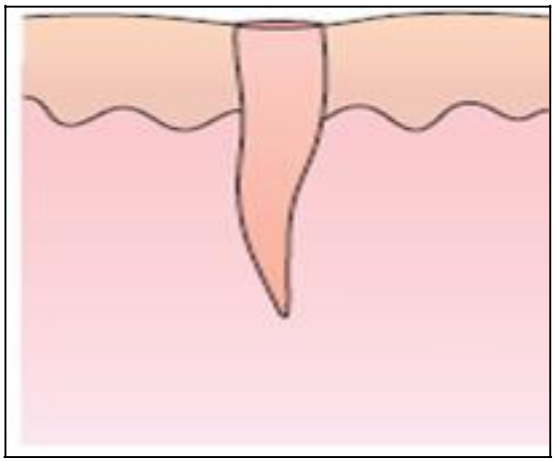


Figure 12. Mature Contracted Scar Angiogenesis & collagen synthesis

Factors affecting Wound Healing

General factors

- Age- younger age faster healing
- Nutrition – Decreased Vitamin, protein- delays wound healing
- Corticosteroids
- Anemia

- Diabetes
- Uraemia
- Jaundice
- Malignancy

Management of diabetic foot ulcers

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

1. Appraise problem
    a. Careful inspection with emphasis on webspaces and back of heels.
    b. Record pulses, venous filling time, rubor
    c. Record sensation.
2. Describe lesion
3. Describe Necrotic tissue, probe sinuses with sterile probe to determine the extent of disease.
4. Culture pus for aerobic and anaerobic organisms
5. Begin broad spectrum antibiotic until appropriate antibiotics can be given according to culture and sensitivity.
6. Medical Management of Diabetes - Blood sugar monitoring and anti diabetic measures to achieve good glycemic control, Doppler study of vessels.
7. X-ray both feet to exclude osteomyelitis.
8. No weight bearing
    a. Hospitalize with absolute bed rest when indicated.
    b. Crutches or walker when feasible.
9. Surgical Management of the Problem
    a. No soaks

b. Antibiotics

c. Medical Management of diabetes

d. Dressing change atleast once daily.

e. Surgical debridement, frequently if necessary.

f. Consideration for possible arterial reconstruction

g. Drainage or open amputation.

10. Rehabilitation

a. Podiatrist for patient education, preventive maintenance orthotics, healing sandals and special shoes.

b. Nutritionist to advice on diet needs.

c. Surgeon to ensure proper wound healing and proper prosthetics

d. Physician to make final decision about diabetes management.

e. Psychiatrist to return to normal activity.

Principles of Surgical Management[53,69]

1. Early recognition and prompt intervention.
2. Control of blood glucose
3. Complete rest of injured area.
4. Careful but complete debridement and drainage of all involved areas.
5. Appropriate antibiotic coverage
6. Wound care and dressings
7. Appropriate vascular reconstructions
8. Careful follow up including podiatric appliances and modified footwear.
9. More experienced consultation as necessary.

Different types of debridement for patients with diabetic foot ulcer[51]

Method	Explanation	Advantages	Disadvantages
Surgical or Sharp	Callus and all nonviable soft tissues and bone remove from the open wound with a scalpel, tissue nippers, curettes, and curved scissors. Excision of necrotic tissues should extend as deeply and proximally as necessary until healthy, bleeding soft tissues and bone are encountered	Only requires sterile scissors or a scalpel, so is cost-effective	Requires a certain amount of skill to prevent enlarging the wound
Mechanical	This method includes wet to dry dressings, high pressure irrigation, pulsed lavage and hydrotherapy, and commonly used to clean wounds prior to surgical or sharp debridement	Allows removal of hardened necrosis	It is not discriminating and may remove granulating tissue; It may be painful for the patients
Autolytic	This method occurs naturally in a healthy, moist wound environment when arterial perfusion and venous drainage are maintained[18	It's cost-effective; It is suitable for an extremely painful wound	It's time consuming and may require an equivocal time for treatment
Enzymatic	The only formulation available in the United Kingdom contains Streptokinase and Streptodornase (Varidase Topical® Wyeth Laboratories). This enzyme aggressively digests the proteins fibrin, collagen and elastin, which are commonly found in the necrotic exudate of a wound	They can be applied directly into the necrotic area	Streptokinase can be systemically absorbed and is therefore contraindicated in patients at risk of an MI; It's expensive
Biological	Sterile maggots of the green bottle fly (Lucilia sericata) are placed directly into the affected area and held in place by a close net dressing. The larvae have a ferocious appetite for necrotic material while actively avoiding newly formed healthy tissue	They discriminate between the necrotic and the granulating tissue	There may be a reluctance to use this treatment by patients and clinicians; It's expensive

Debridement is often a key element in effective wound care. Recently, the wound healing community endeavored to create guidelines in an effort to help standardize debridement.[70,71]

The frequency and aggressiveness with debridement varies greatly from practitioner to practitioner. Training of the clinician, available resources and fee for service can factor into how frequently we debride an ulcer. The fee-for-service model can potentially increase the frequency and extent of debridement. As healthcare moves from a fee for service model to a value-based paradigm, providing the most high quality, cost-effective treatment is all that matters. We must learn to heal wounds quicker and with lower cost. Improving our techniques and protocols for effective debridement will help us meet this challenge. Value-based medicine demands superior outcomes.[71]

Additionally, the chronicity of the wound and amount of bioburden are factors that reduce normal wound healing. Chronic ulcers may have developed secondary to a myriad of etiologies including trauma, surgery, pressure, metabolic, venous and arterial etiologies, and diabetic neuropathy. Bioburden is like a wall that allows bacteria to be protected from the host's defenses. Biofilms are often recalcitrant to routine surgical debridement.[72]

The three most prevalent agents to reduce bioburden are iodine, silver and honey. Iodosorb (Smith and Nephew) is able to reduce bioburden, control exudate and provide a measure of debridement. The use of silver and honey products is well documented. Maggot therapy is another modality that can help reduce bioburden while also debriding the wound.

Key Benefits Of Debridement

Importance of debridement

Debridement has the following purposes.[73,74]

- Debridement reduces bioburden to help control or reduce infection. Even if an ulcer is not "infected," the bacterial bioburden causes increased local inflammation.
- Debridement allows more accurate visualization of the wound base and edges, which allows for more precise staging.
- Debridement removes necrotic/non-viable tissue, which impedes wound healing, causes protein loss and can be a nidus for infection.
- Debridement stimulates new circulation (angiogenesis) and allows adequate oxygen delivery to the wound.
- Debridement removes undermining and tunneling, and may help reduce abscess formation.
- Debridement releases healing growth factors at the edge of the wound.
- Debridement prepares the wound bed by leaving only tissues that are capable of regenerating.

When to Debride ?

Studies by Steed, Williams and their respective colleagues found that sharp debridement of wounds resulted in increased healing rates in comparison to wounds that were not debrided.[75,76] These well-known studies validated our debriding of wounds but again, are we debriding too much?

There are no concrete guidelines on wound debridement. The European Wound Management Association put out a nearly 50-page document on debridement.[70] They recommend a debridement algorithm based on the consensus opinion of the authors. The reality is that there is a lack of standardized guidelines for wound debridement.

A consensus guidance from the United Kingdom in 2010 attempted to address this lack of standardization.[77] In terms of debridement, the authors recommended that prior to debridement, the clinician should consider the following:

- What is the goal of debridement?
- How quickly does one need to achieve this goal?
- What is the best modality for accomplishing the debridement?

Not all wounds need debridement and we as wound care specialists need to avoid tunnel vision. A well-adhered eschar that is not infected will be better served if we leave it alone. If the wound has minimal devitalized tissue, even the most skilled doctors cannot be 100 percent sure of the precision of their debridement.[71]

Different Types Of Debridement

Surgical (sharp) debridement.

Surgical debridement is the quickest and most efficient method of debridement. It is the preferred method if there is concern of infection or abscess. This technique is quick and selective, but very user dependent.[71]

Mechanical debridement.

In mechanical debridement, a saline-moistened dressing dries overnight and adheres to the dead tissue. Removing the dressing pulls away the dead tissue. This process is one of the oldest methods of debridement. It can be very painful because the dressing can adhere to living as well as non-living tissue. Whirlpool therapy, gauze, paraffin and monofilament fiber pads are other examples of mechanical debridement.[71]

Enzymatic debridement

This technique makes use of certain enzymes and other compounds to dissolve necrotic tissue. It is highly selective. Proteolytic enzymes hydrolyze peptide bonds, which helps to facilitate removal of non-viable tissue from the wound. These enzymes work synergistically with the wound's endogenous enzymes. One then places a moist dressing over the wound. Enzymatic debridement is faster than autolytic debridement but more conservative than sharp surgical debridement.[71]

Autolytic debridement

This process takes advantage of the body's own endogenous enzymes to remove necrotic tissue slowly. The key to the technique is keeping the wound moist as these dressings are occlusive, which helps to saturate the wound. These dressings help trap wound fluid that contains the growth factors, enzymes and immune cells that promote wound healing. Autolytic debridement is more selective than any other debridement method but it also takes the longest time to work. It is inappropriate for

wounds that have become infected. Patients usually change these dressings every two to three days. It is necessary to take precautions to protect the periwound from maceration.[71] e.g. hydrocolloids, hydrogels, highly absorptive, hydrofibers and iodine-based preparations such as Iodosorb.

Larval therapy

Maggot therapy (biosurgery) is a form of biological debridement known since antiquity. The larvae of Lucilia sericata (green bottle fly) secrete enzymes that break down necrotic tissue into a liquid. The larvae then ingest this liquid. The maggot secretions also contain antibacterial substances. They also promote wound healing and amplify human fibroblast and chondrocyte growth. The method is rapid and selective although patients are usually reluctant to submit to the procedure. Typically, one would place larvae in the wound bed twice a week and leave them in place for 24 to 72 hours with a recommended dose of 10 to 15 larvae per cm^2. One can also utilize maggot therapy with a biobag, which contains the larvae and prevents escape.[71]

Ultrasound debridement

Depending on frequency and intensity, ultrasound can exert a range of effects on ulcers. This versatility allows one to use ultrasound on nearly every type of wound. The benefits of ultrasound are evident in the cavitation effect and the direct stimulation of cells. In cavitation, bursting microbubbles assist in the fibrinolytic separation of denatured protein, which results in selective debridement and fragmentation of non-viable tissue. Cavitation also can have a direct bactericidal effect.[71]

The stimulation of cells (via fluid shear stress) causes the release of nitrous oxide. This subsequently results in resolution of the vasospasm, thereby increasing blood flow around the wound. Additionally, fibroblasts, macrophages and endothelial cells are stimulated.[71,78]

Examples of ultrasound debridement products include Qoustic Wound Therapy System (Arobella Medical) and SonicOne (Misonix). The Qoustic Wound Therapy System delivers focused ultrasonic energy as it lightly contacts the wound bed, gently separating and removing unwanted tissue while preserving healthy granulation tissue.[71]

Hydrosurgery.

Jet lavage debridement is the evolution of wound irrigation. Clinicians can use the irrigation from hydrosurgery to physically remove debris, loose tissue, etc., from the wound. There are a number of hydrosurgery products. The versatility of hydrosurgery intensities enables clinicians to use these devices on almost all types of wounds.[71]

Examples of these devices include MIST therapy, is a painless, low frequency, low intensity, non-thermal, non-contact ultrasound-generated mist. Promoting healing by mechanical cell stimulation, MIST Therapy allows clinicians to perform gentle wound debridement that reportedly reduces the wound's bacterial bioburden and increases angiogenesis.[71]

Another potential benefit is the possible use of antibiotic/antiseptic solutions (super-oxidized solutions and polyhexanide solutions) instead of saline. When one

uses a hydrosurgical device in conjunction with antiseptic irrigation, it may act as a physical and biological debrider.[71]

Super-oxidized solution (SOS) is a hypotonic solution that contains hypochlorous acid, sodium hypochlorite, chlorine dioxide, ozone, hydrogen peroxide and sodium chloride. It is an electrochemically processed aqueous solution manufactured from pure water and sodium chloride. Reactive species of oxygen and chlorine (which have formed via electrolysis) create an unbalanced osmolarity. This disparity in osmolarity subsequently causes damage to the integrity of the cell membrane and then reacts and denatures the lipids and proteins of single cell organisms. This is a direct result of the osmolarity difference between the ion concentrations of the solution and single cell organism.

Multicellular organisms are not prone to such osmolarity changes, which is why these solutions are safe to use on the wound. Polyhexanide is a positively charged polymer that works against negatively charged microorganisms. It is able to penetrate slough and bioburden to stimulate wound healing.

Products like DermaPACE and the Qoustic device give us new tools to stimulate wound healing without the trauma of sharp debridement. One should consider alternative methods to sharp surgical debridement when the wound bed is covered in fibrin or slough, or if the wound is of partial thickness and the wound edges are not clearly demarcated.

Debridement is only a portion of the equation for a wound to heal and a multidisciplinary team approach is essential for wound healing. Without proper nutrition, effective management of comorbidities, control of any infection and

providing for adequate vascularity, the wound cannot function properly. Until we restore this delicate balance, the wound will not heal. The aggressive implementation of offloading devices, the timely application of the "best" wound dressings that can absorb exudate and the appropriate use of biologics to stimulate wound healing are key elements to restore this balance and facilitate an environment for wound healing.

Papain-urea-based Combinations

A well-known and widely used enzymatic system is the papain-urea combination.[79-81] In this system, papain is used to attack and break down any protein containing cysteine residues. This property of papain renders the combination quite nonselective because most proteins, including growth factors, contain cysteine residues. Collagen contains no cysteine residues and is thus unaffected by papain.[82] The urea component of the most widely used of these combinations will also attack a wide variety of proteins. However, urea's role in this enzymatic combination is to facilitate the proteolytic action of papain by altering the three-dimensional structure of proteins and disrupting their hydrogen bonds. Urea also plays a role in the reduction of disulfide bridges; as the disulfide bridges are reduced, cysteine residues become exposed and are, therefore, more susceptible to the action of papain.[**83**] It should be noted that the combination of papain and urea is probably twice as effective in protein digestion as papain alone.[84] Also, and this may be applicable to other enzyme preparations, hydrogen peroxide can block the effect of papain-urea preparations, as can other commonly used treatments and agents for chronic wounds, such as silver sulfadiazine, gentamicin, and alcohol-based products.[85]

An advantage of the papain-urea combination may be nonspecific bulk debridement within a broad pH range (3.0-12.0). However, perhaps because of the nonselective feature of this enzymatic preparation, a prominent inflammatory response is associated with its use in chronic wounds. This inflammatory response, together with break down of still viable components of the wound bed, is perhaps the reason for the considerable pain often associated with the use of these agents. The effect of chlorophyllin on viable tissue is not known, but it is felt that this additional ingredient in the final combination of papain-urea has no detrimental effect and does not increase pain. The papain-urea preparations have been used clinically for decades, especially in pressure ulcers. The available literature indicates that these debriding systems are effective when properly used, especially if one keeps in mind that they cannot substitute for surgical debridement when that is required.[85]

In summary, the nonselective features of these combinations offer advantages and disadvantages. Bulk and quick debridement, without having to worry about affecting viable tissue, might be an advantage in certain situations, particularly when the affected area is insensate and thus not able to experience the pain associated with this preparation.[85]

Others Sources of Enzymes

Animal-derived enzymes.

One class of enzymes used or considered for use as debriding agents is derived from animal sources. Included in this class of enzymes are fibrinolysin, desoxyribonuclease, trypsin, and chymotrypsin. On a commercial scale, all of these

enzymes are typically derived from bovine sources. Fibrinolysin is typically derived from bovine plasma. This enzyme, when activated, specifically attacks and breaks down the fibrin component of blood clots and fibrinous exudates. Desoxyribonuclease is derived from bovine pancreatic tissue and acts specifically on the nucleoprotein components of purulent exudates. These two enzymes have been combined together in a product known as Elase, which is available in some European countries. Studies have been conducted with this product and its components with results that suggest it may be somewhat effective as a debriding agent in uncomplicated ulcers but not any more effective than placebo in complex wounds.[86]

Plant-derived enzymes.

Enzymes useful for debridement applications have also been recovered from various plants. Bromelain is a group of enzymes derived from the stem of pineapple plants that contains three cysteine proteinases. This mixture of enzymes is effective at breaking down a variety of devitalized tissue substrates over a pH range of 5.5 to 8.5. Papain is an enzyme derived from the fruit of the papaya tree (Carica papaya). Papain is a nonspecific cysteine proteinase (an enzyme that contains a cysteine residue at the active site) that is capable of breaking down a wide variety of necrotic tissue substrates over a wide pH range (3.0 to 12.0). Ficin is an enzyme similar to papain that has activity against a wide variety of protein substrates.[86]

Microbially produced enzymes.

Besides enzymes that are normally obtained from eukaryotic sources, there are also several microbially produced enzymes that may be used in debridement.

The discussion pertains only to those that are naturally produced by bacteria and does not include eukaryotic enzymes that may be produced through recombinant means in prokaryotic expression systems. Sutilains are water-soluble mixtures of serine proteinases derived from the bacterium Bacillus subtilis. These enzymes are relatively nonspecific in their action and are capable of breaking down a variety of necrotic tissue types over an optimal pH range of 6.0 to 6.8. Perhaps the most widely known microbially produced enzymes that are in current use as debriding agents are the collagenases. Another enzyme that is currently being explored for possible use as a debriding agent is vibriolysin. Vibriolysin is another metallopeptidase derived from the bacterium Vibrio proteolyticus and has been found to be very active for digesting collagen.[86]

Physical and chemical characteristics and mode of action.

Papain, the proteolytic enzyme from the fruit of Carica papaya, is an enzyme with potent activity against denatured (nonviable) protein. At the same time, clinical and laboratory experience has demonstrated that the enzyme does not harm the viable tissue surrounding the wound.28 Papain, combined with urea, produces a very effective debriding agent as demonstrated by in-vitro studies. The principle components of wound eschar include fibrin, collagen, and elastin. An in-vitro efficacy study has shown that papain-urea can effectively digest these eschar proteins. Fibrinolysis studies have demonstrated that papain urea shows enhanced ability to digest fibrin compared to either papain or urea alone in the papain urea ointment base.[86]

Functional proteins typically exist with a high degree of tertiary structure (folds and other three-dimensional structures) that contributes to their functionality. This three-dimensional structure is maintained by hydrogen bonds within the protein. Urea, a small nonionic molecule, is capable of interfering with these bonds causing the protein to essentially relax. In addition, experimental evidence suggests urea may cause disruption of some of the disulfide bonds within proteins to expose particular thiol groups (–SH), which may serve as activators of papain. Papain itself is unusually resistant to the effects of urea and is stable in the level of urea present in papain-urea.[86]

These studies also demonstrated that papain-urea is considerably more active in digesting denatured collagen than native collagen. These studies suggest that the papain/urea debriding ointment could effectively cleave the denatured collagen found in nonviable tissues with very limited action against native protein in surrounding viable tissues.[86]

The debriding efficacy of the enzyme may depend on its delivery vehicle. The same enzyme formulated in different ointment bases under different manufacturing specifications could result in very different proteolytic activity (efficacy). Papain-urea is formulated using a proprietary emulsion system developed to be very compatible with papain and urea. It provides all the conditions necessary for the enzyme to be active. Papain is found to release from the formulation easily with full activity. The formulation also maintains the stability of papain for its labeled shelf life.[86]

The presence of penicillin and sulfonamides does not inhibit the proteolytic action of papain, whereas Terramycin, Aureomycin, and Chloromycetinmay inhibit protein digestion.[86]

Clinical Experience with Papain-Urea Debriding Preparations

The long clinical history of the use of papain or papain-urea preparations for wound debridement clearly demonstrates the effectiveness of this enzyme as a debriding agent. In 1879, Wurtz and Bouchut first coined the term papain to describe the purified proteinase derived from papaya. By the 1880s, various pharmaceutical preparations containing this enzyme were available for many indications, such as eczema, psoriasis, and oral syphilitic ulcers. Modder in 1888 applied papain to speed the separation of slough from chronic, slow healing ulcers. In 1901, Kilmer, in a monograph on the pharmaceutical use of papaya fruit, noted a similar use of papaya paste in infected wounds by the indigenous peoples of areas where papaya was grown.36 Since that time, papain has been used successfully as a debriding agent in the treatment of a number of different wound types.[86]

Chronic wounds

In 1940, Glasser reported the successful use of papain treatment in 58 cases of sloughing wounds.37 The action of urea to relax folded proteins and render them more susceptible to attack by papain was subsequently recognized, and debridement preparations containing papain-urea combinations were developed.[86]

The use of a papain-urea debridement preparation on 37 patients with ulcers resistant to conventional therapy. The types of ulcers evaluated in this study included pressure ulcers of the scalp, decubitus ulcers of the sacrum, ischium, or

trochanters, traumatic leg ulcers due to poor circulation, and diabetic leg ulcers. Some of these patients had previously been treated unsuccessfully for periods ranging from 24 days to 3 years. Treatment with this preparation resulted in lesions that were clean and beginning to granulate, generally within 5 to 12 days. The results from bacterial cultures taken prior to debridement and again when the wound bed appeared to be clean and granulating showed that papain-urea debridement was not affected by the presence of various wound microbes. The results also demonstrated an inability to culture organisms from the wound bed in 11 of the patients following debridement. No adverse reactions to the medication were observed. This study concluded that daily application of this preparation was effective and allowed the nursing staff more time to devote to other patients, thereby making it more economical than other treatments requiring multiple daily applications.[86]

The utilization of this type of conservative approach to wound debridement as being desirable in nursing home settings, such as where the study was undertaken. In this 26-person study, a proportion of the wounds were treated with papain urea (n = 14) once daily for four weeks or until complete debridement was achieved. The remaining wounds were treated with a competitive product. Morphometric measurements were used to follow the wound size and the amount of nonviable tissue associated with the wounds. In this study, papain urea was found to be effective in quickly debriding the nonviable tissue. As illustrated in, only approximately 20 percent of the eschar present at the initiation of treatment was present after one week of treatment. The rapid debridement was associated with a concomitant appearance of granulation tissue, as determined by clinical assessment.

During the conduct of the study, the authors reported there were no incidents of pain associated with the treatment, and none of the patients withdrew from the study as a result of failure of the treatment regimen. Additionally, the authors did not report any irritation to the surrounding tissue as a result of application of the enzyme preparation to the wounds accompanied by the presumed contact of the drug product with surrounding healthy tissue. It is suggested that debridement with papain urea was, "a safe and effective alternative to surgical debridement."[86]

There is extensive historical data supporting the use of papain-urea preparations as safe wound debridement products. In addition, in an independent study conducted in 1995, papain urea was applied to 59 human subjects to evaluate the level of irritation and/or sensitization produced following multiple, repeated applications (10 applications per subject). No visible signs of erythema or edema were noted for any papain urea treated site relative to its corresponding untreated control site on any subject. Similarly, challenge testing conducted following a 14-day induction phase did not produce signs of sensitization in any of the subjects. The conclusion from this study was that papain urea did not indicate a potential for dermal irritation and/or sensitization.[86]

SOS may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds. These solutions are electrochemically processed aqueous solutions manufactured from pure water and sodium chloride (NaCl). During the electrolysis process, water molecules are pulled apart, and reactive species of chlorine and oxygen are formed. Different super-oxidized solutions have different properties. Increased acidity or alkalinity and high concentrations (> 100 ppm) of free available chlorine (FAC) correlate with increased corrosiveness and

toxicity of a solution. Another problem with these solutions has been stability, which can range from a few hours to several days.[87]

Recently, a neutral pH SOS became available in Europe. According to the manufacturer, this solution has a low FAC (< 80 ppm) and is stable for more than 1 year. This solution has shown broad antimicrobial activity even against antibiotic-resistant strains. It has also been reported that this solution does not induce skin, dermal, or systemic toxicities in animal models. Preliminary data in humans also suggest efficacy and safety.[87]

Use of Super Oxidized Solution is a new concept in wound management. This is a hypotonic solution with an osmolarity of 13 mOsm/kg and containing Hypochlorous acid, Sodium hypochlorite, Chlorine dioxide, Ozone, Hydrogen peroxide, and Sodium chloride. Super Oxidized Solution is an electrochemically processed aqueous solution manufactured from pure water and sodium chloride. During this electrolysis process reactive species of oxygen and chlorine are formed. These released reactive species creates an unbalanced osmolarity, so that it damages the integrity of the cell membrane, then reacts and denatures the lipids & proteins of single cell organisms.[88] This is because of a direct result of the osmolarity difference between the ion concentrations of the solution and single cell organism. Multicellular organisms are not prone to such osmolarity changes.[89]

Treatment with SOS reduces the microbial flora, is less painful during cleaning and debridement procedures. It can be used safely in various conditions such as diabetic foot ulcers, venous stasis ulcers, bed sores, burns, cuts, abrasions, post operative infective wounds, cellulitis and abscesses.

The concept of wound healing with SOS, a novel and effective mode of treatment. The efficacy of SOS in different types of wounds was found to be superior than the conventional method of treatment with povidone iodine.[8]

Study conducted by Dr. Luca Dalla Paola on 218 patients suffering from chronic diabetic foot ulcers 110 patients were treated with SOS and 108 patients with povidone iodine. The mean healing time was lower in the SOS group (45±14) days v/s (58±20) days in betadine group.[87]

Gutierrez in his study to explore various applications of SOS concluded that the moistening effects and minimum toxicity found with the use of this SOS made it a good choice for wound care management.[90]

Papain has been utilized in different ways. In the USA, it is associated with urea and in Brazil it is employed using a natural approach, by placing the papaya fruit itself on the wound, in saline solutions and in the form of paste or gel,[88,91] Papain is one substance which has been used in different manners for enzymatic debridement, including naturally, using the papaya fruit itself, as extracts dissolved in saline solution, or in gels or in paste.

In Brazil, the first studies on debridement using papain were published by Monetta who greatly contributed to this practice. Initially, different amounts of concentrated extracts, generally around 2.5%, were dissolved in saline solution.[95]

Currently the concentrations still vary but are normally around 1% to 3% depending on the experience of each professional.

In the USA, the use of an association of papain and urea has been reported in several studies. Among the benefits of urea are its strong osmotic power which facilitates hydration of the wound.[92]

In a study conducted on 218 patients suffering from chronic diabetic foot ulcers 110 patients were treated with SOS and 108 patients with povidone iodine. The mean healing time was lower in the SOS group (45±14) days v/s (58±20) days in betadine group.[93]

In a study conducted at the hospital Civil de Guadalajana in Mexico in 2004–05 with superficial-partial, deep-partial and full thickness burns the study group was treated with SOS and was compared retrospectively with similar burns at the institution which had been treated with silver solutions/ointments (control group). In this trial only 6 patients received antibiotics in superoxidised group versus 56 in control group. Furthermore hospital stay was reduced by50% in patient treated with SOS group v/s control group.[94]

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 2015 to December 2015.

Study design

The study design was a randomized controlled trial.

Study period and duration

This study was carried out for the duration of one year from January 2015 to December 2015.

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 KLE University's Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Diabetic Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers which are not healed, over a period of > 3 weeks and for which debridement is required for healing Patients, were enrolled.

Sample size

The present study was comprised of 60 Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers which are not healed, over a period of > 3 weeks and for which debridement is required for healing patients divided into two groups of 30 each.

Sampling procedure

As papain urea have proven efficacy in bringing out enzymatic wound debridement .Papain-urea (89.2%) is a better enzymatic debriding agent than others enzymatic agents(82.2%).Papain urea (from 2.4sq.cms to 6.8sq. cms.) promotes faster granulation compared to other enzymatic agent(1.4sq.cms to 3.5sq.cms). In one study they have shown that, diabetic foot ulcer and chronic leg ulcers patients treated with superoxidised solution shows early granulation and rapid epithelisation when compared to betadine group. The mean follow up of 21 days shows that average reduction in wound size and periwound odema/erythma in superoxidised solution group was 70% as compared to 50% in povidone iodine group. Both the group are superior when compare with others enzymatic agent or by conventional method, but as no similar studies have been done which compare papainurea based preparation comparing superoxidised solution, sample size has been taken in accordance with the thumb rule,

Selection criteria

Inclusion

- Diabetic patients aged > 18 years.

- Patients who are suffering from diabetic foot ulcers.
- Ulcers which are not healed over a period of more than 3 weeks and for which debridement is required for healing,
- Patients taking insulin or oral hyperglycaemic both are included in this study.

Exclusion

- **C**hronic non healing wounds of other etiology
- Diabetes Mellitus with gangrenous changes
- Wound with osteomyelitis & other condition like renal failure, generalized debility and other factors which affects wound healing.
- Patient receiving corticosteroids, immunosuppressive agents, radiation or chemotherapy within one month prior to entry into the study were excluded

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 (Annexure I).

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 (Annexure II).

Investigations

The patients underwent following investigations.

- Complete blood count.
- Fasting blood sugar
- Blood Urea
- Serum Creatinine
- X-Ray foot – Antero-posterior and Lateral view
- Tissue culture.

Randomization

The patients were divided into two groups of 30 each viz. Group A and group B based on closed envelope method as below

- First group (Group A) with superoxidised solution.
- Second group (Group B) with papain-urea based preparation.

Treatment

All the patients underwent debridement of wound. Empirical antibiotics viz. Cefotaxim and Metranidazole or Ceftriaxone and Metranidazole were started and changed to sensitive antibiotics after culture and sensitivity report. In both the groups povidine iodine was used as an antiseptic. The dressing and topical management was done as below.

Group A

Dressing with superoxidised solution is done.

Group B

Dressing with papain urea based preparation is done.

Same antibiotic were used for both the groups. Dressings were done using same technique – cleaning with saline and application of ointment/spray (superoxidised solution /papain – urea) and putting a dressing. The time since the last dressing changed was consistent from one assessment to the next. Application of ointment in both the groups was done once daily in the following manner:

- Prior to application, the lesion was cleaned of debris and digested material by gently rubbing with gauze pad by normal saline.

- Whenever infection is present, an appropriate topical antibiotic powder should be applied to the lesion prior to the application of Ointment.

- Ointment was applied directly to deep lesions with a wooden tongue depressor or spatula. For shallow lesions, Ointment was applied on sterile gauze pad, which was then applied to the wound and properly secured.

- All excess ointment was removed each time dressing was changed.

- Use of ointment was terminated when debridement of necrotic tissue was complete and granulation tissue was well established or for a maximum period of three weeks or 21 days.

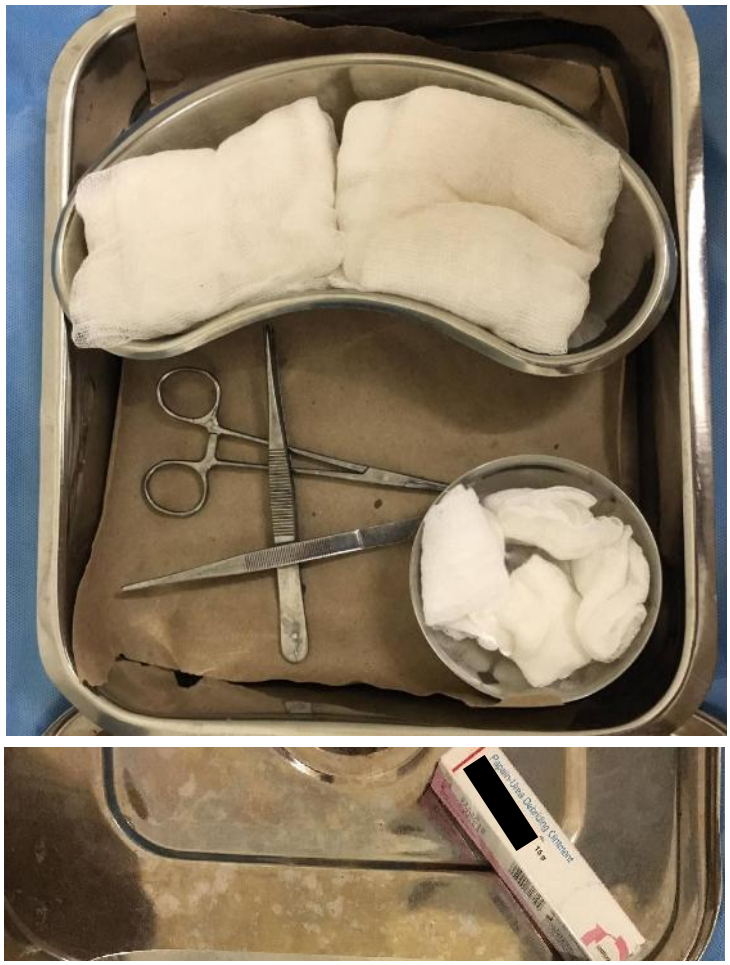
Outcome variables

- 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. Area of the slough was assessed at the beginning, 5^{th}, 10^{th} and 21^{st} days.

- Assessment of wound - Ulcer size was assessed at the end of every second and fourth week. Ulcer mapping was made and the size recorded by superimposing a gauze over the ulcer and thus assessing the largest dimensions of the ulcer. Size was measured twice and the mean of the both measurements were considered as the size of the wound. Wound was also observed for granulation, tissue quality, discharge and control of infection at the end of second and fourth week.



Photograph 1. Dressing material with papain urea

Follow up

The patients were evaluated at beginning of dressing (after randomisation), one, two and three weeks.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel Spreadsheet. The categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test and Fisher's exact test. Continuous data was expressed as mean ± standard deviation and the independent sample 't' test was used for comparison. A 'p' value of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

RESULTS

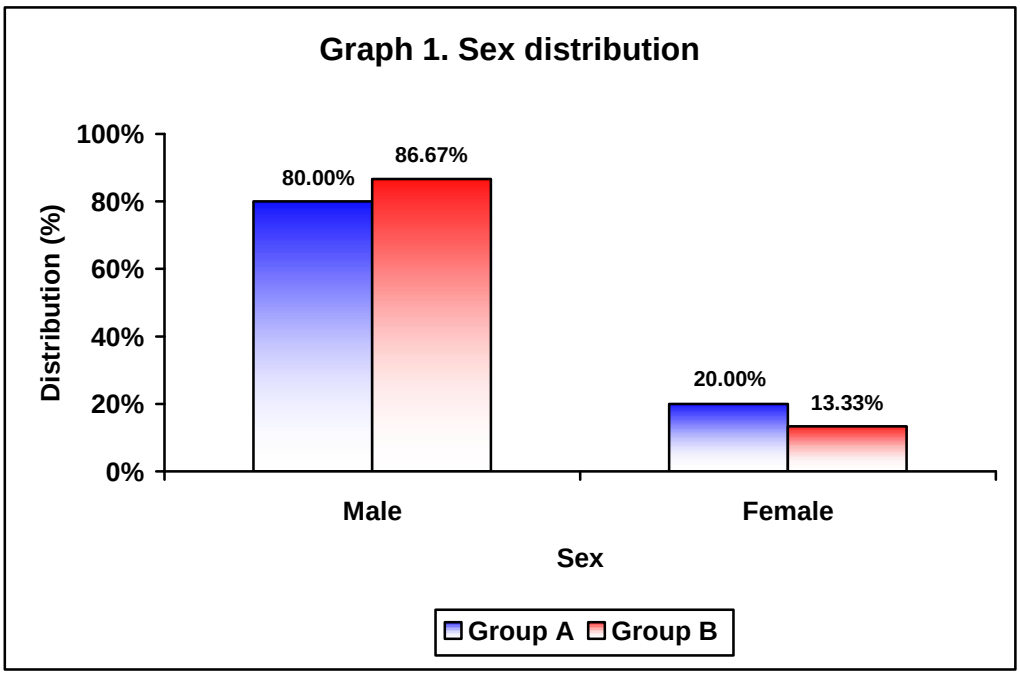
This randomized controlled trial was done in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi over a period, from January 2015 to December 2015. A total of 60 Diabetic Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers which are not healed, over a period of > 3 weeks and for which debridement is required for healing were enrolled. These patients were divided into two groups of 30 each that is First group (Group A) with superoxidised solution and Second group (Group B) with papain-urea based preparation.

The data was analysed and the final results and observations were tabulated as below.

Table 1. Sex distribution

Sex	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Male	24	80.00	26	86.67
Female	6	20.00	4	13.33
Total	**30**	**100.00**	**30**	**100.00**

p = 0.488

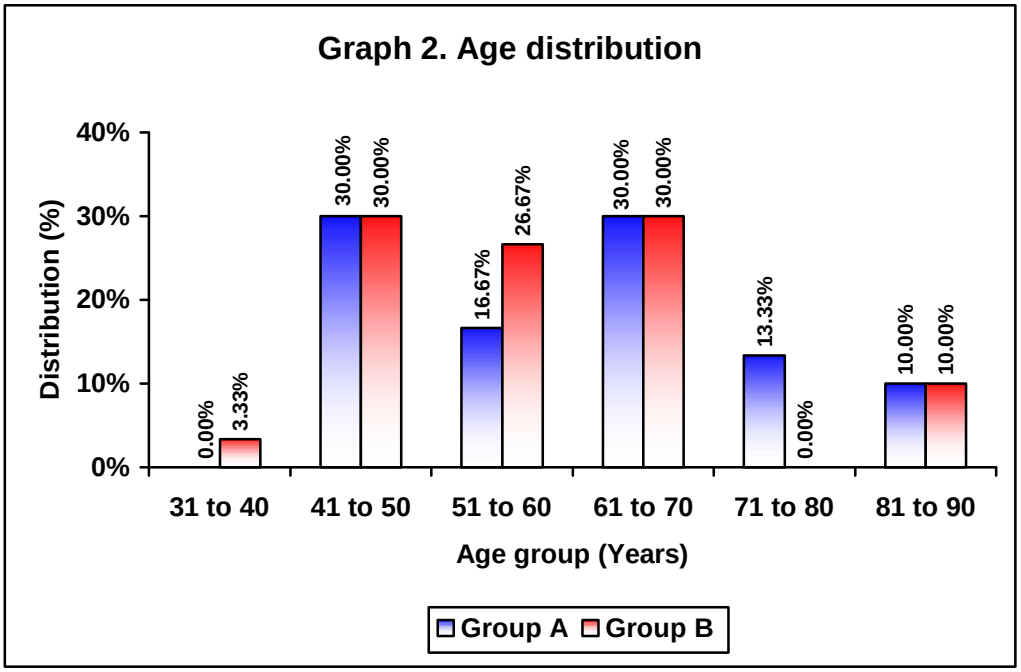


In the present study 80% in group A and 86.67% of the patients in group B were males. The male to female ratio was 4:1 in group A and 6.5:1 in group B. However the sex distribution was comparable in group A and group B. (p=0.488)

Table 2. Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
31 to 40	0	0.00	1	3.33
41 to 50	9	30.00	9	30.00
51 o 60	5	16.67	8	26.67
61 to 70	9	30.00	9	30.00
71 to 80	4	13.33	0	0.00
81 to 90	3	10.00	3	10.00
Total	**30**	**100.00**	**30**	**100.00**

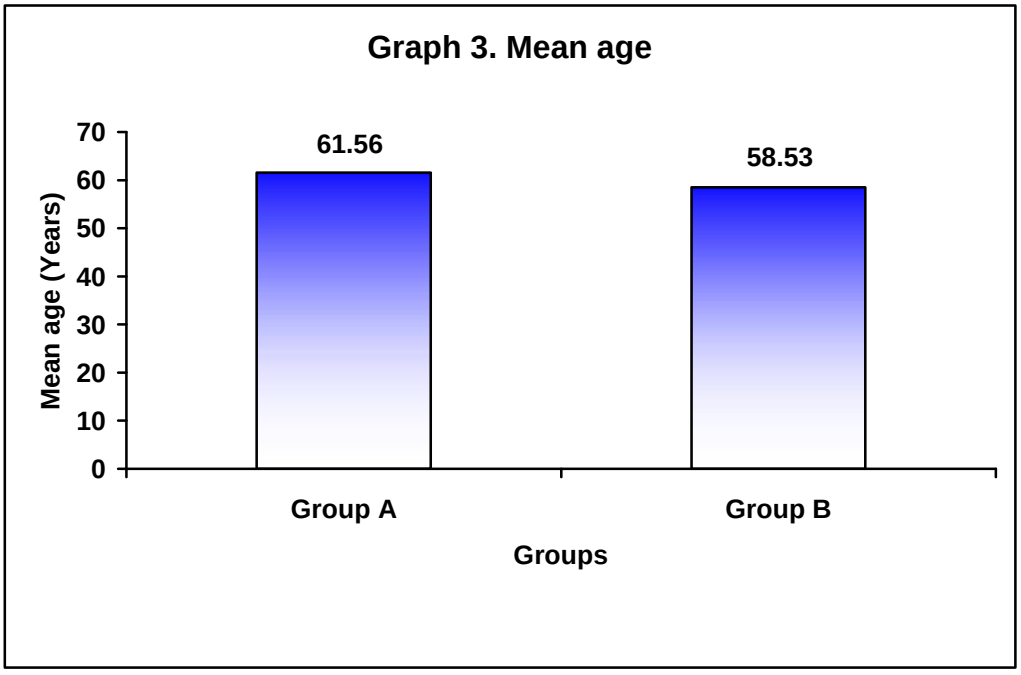
p = 0.362



In this study most of the patients were aged between 41 to 50 years and 61 to 70 years in both the groups (30% each) (p=0.362)

Table 3. Mean age

Variables	Group A (n=30)		Group B (n=30)		t value	DF	p value
	Mean	SD	Mean	SD			
Age (Years)	61.56	13.00	58.53	11.40	0.960	58	0.341



In the present study mean age in group A was 61.56 ± 13.00 years compared to 58.53 ± 11.40 years in group b. However this difference was statistically not significant (p=0.341)

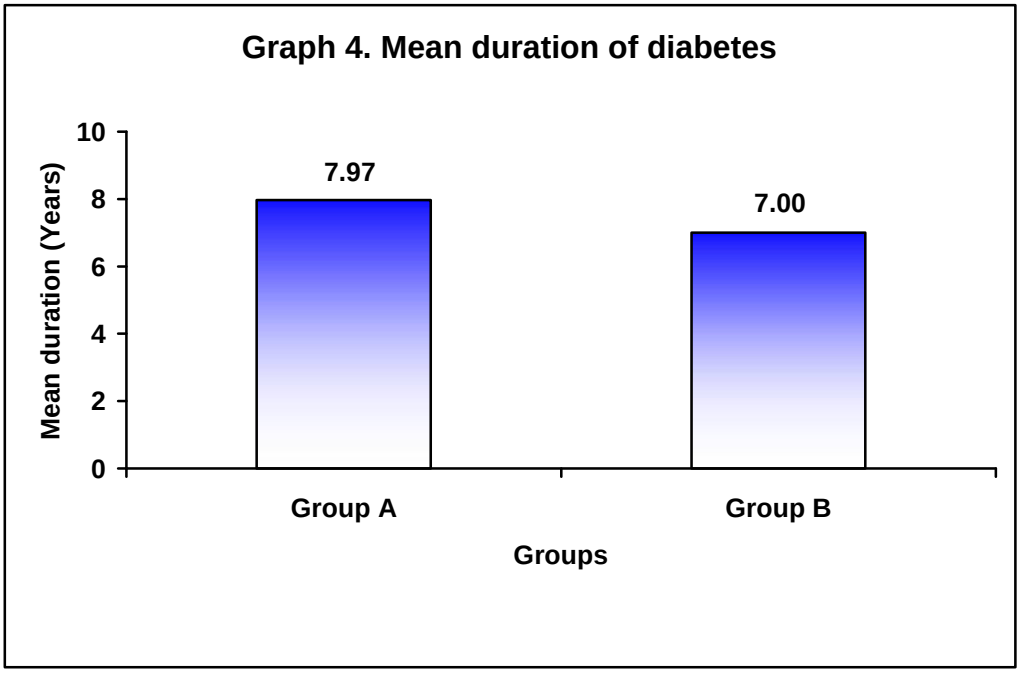
Table 4. Diabetic characteristics of the study population

Variables	Findings	Group A (n=30)		Group B (n=30)		p value
		No	**%**	**No**	**%**	
Type	Type 1	9	30.00	7	23.33	**0.559**
	Type 2	21	70.00	23	76.67	
	Total	**30**	**100.00**	**30**	**100.00**	
Duration	5 or less	1	3.33	0	0.00	**0.817**
(Years)	6 to 10	3	10.00	4	13.34	
	11 to 15	11	36.67	13	43.33	
	> 15	15	50.00	13	43.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Medication	Insulin	24	80.00	28	93.33	**0.129**
	OHA	6	20.00	2	6.67	
	Total	**30**	**100.00**	**30**	**100.00**	

The diabetic characteristics of the study population are as shown in table 4. It was observed that, majority of the patients in group A (70%) and group B (76.67%) had type 2 diabetes mellitus (p=0.559). Most of the patients in group A (50%) and in group B (43.33%) presented with duration of > 15 years (p=0.817). While, majority of the patients in both the groups that is, 80% in group A and 93.33% in group B were on insulin (p=0.129).

Table 5. Mean duration of diabetes

Duration	Group A (n=30)		Group B (n=30)		t value	DF	p value
	Mean	SD	Mean	SD			
Duration (years)	7.97	5.65	7.00	4.18	0.756	58	0.453



The mean duration of diabetes in group A was slightly high (7.97± 5.65 years) compared to group B (7.00 ± 4.18 years). However this difference was statistically not significant (p=0.453).

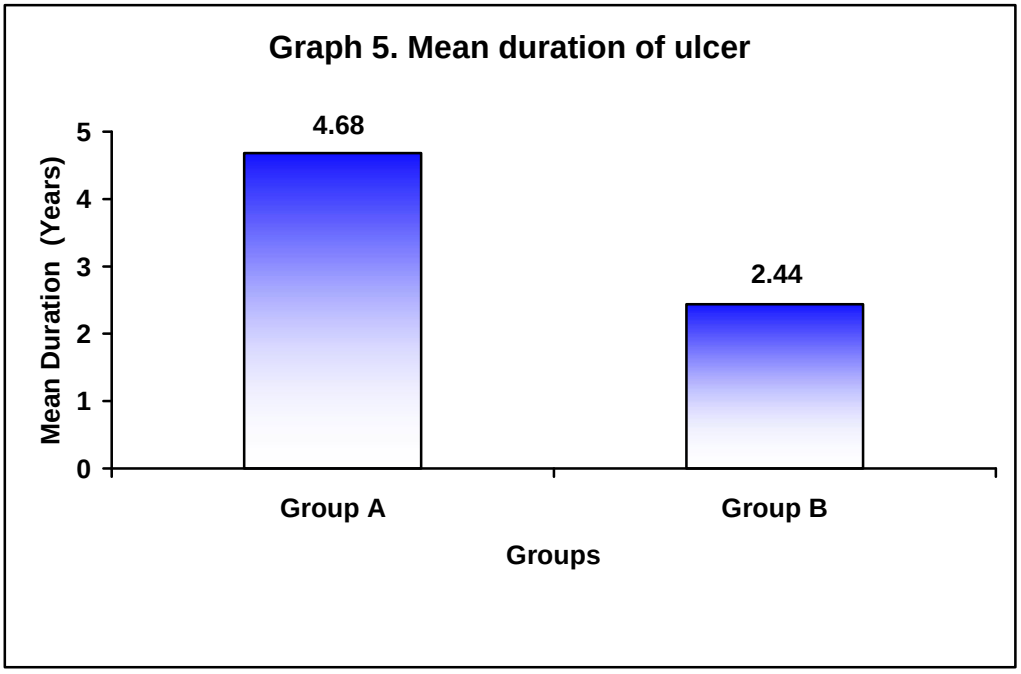
Table 6. Comparison of ulcer characteristics

Variables	Findings	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Mode	Traumatic	17	56.67	18	60.00	**0.684**
	Spontaneous	12	40.00	9	30.00	
	Pressure	1	3.33	2	6.67	
	Others	0	0.00	1	3.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Duration (months)	1 or less	16	53.33	19	63.33	**0.792**
	2 to 12	13	43.33	10	33.33	
	> 12	1	3.33	1	3.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Discharge	Present	5	16.67	2	6.67	**0.212**
	Absent	25	83.33	28	93.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Site	Left	9	30.00	11	36.67	**0.584**
	Right	21	70.00	19	63.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Shape	Oval	6	20.00	11	36.67	**0.348**
	Circular	16	53.33	12	40.00	
	Irregular	8	26.67	7	23.33	
	Total	**30**	**100.00**	**30**	**100.00**	

The comparison of ulcer characteristics is as shown in table 6. It was observed that, most of the ulcers had traumatic mode of onset (56.67% in group A vs. 60% in group B; p=0.684). Most of the ulcers had duration of ≤ 1 month (53.33% in group A and 63.33% in group B; p=0.792). Discharge was absent in most of the ulcers (83.33% in group A vs. 93.33% in group B; p=0.212).

Table 7. Mean duration of ulcer

Duration	Group A (n=30)		Group B (n=30)		t value	DF	p value
	Mean	SD	Mean	SD			
Duration (years)	4.68	9.08	2.44	4.48	1.212	58	0.232



In the present study, the mean duration of ulcer in group A was slightly high (4.68 ± 9.08 months) compared to group B (2.44 ± 4.48 months). However this difference was statistically not significant (p=0.232).

Table 8. Comparison of floor

Intervals	Floor	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Day 10	Granulation	1	3.33	2	6.67	**0.612**
	Slough	29	96.67	28	93.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 21	Granulation	14	46.67	22	73.33	**0.035**
	Slough	16	53.33	8	26.67	
	Total	**30**	**100.00**	**30**	**100.00**	

In this study on day 10 wound observations revealed majority of the wounds with sloughy floor in group A (96.67%) and group B (93.33%) (p=0.612). While on day 21, significantly higher number of patients (73.33%) in group B had granulation compared to group A (46.67%). This difference was statistically significant (p=0.035)

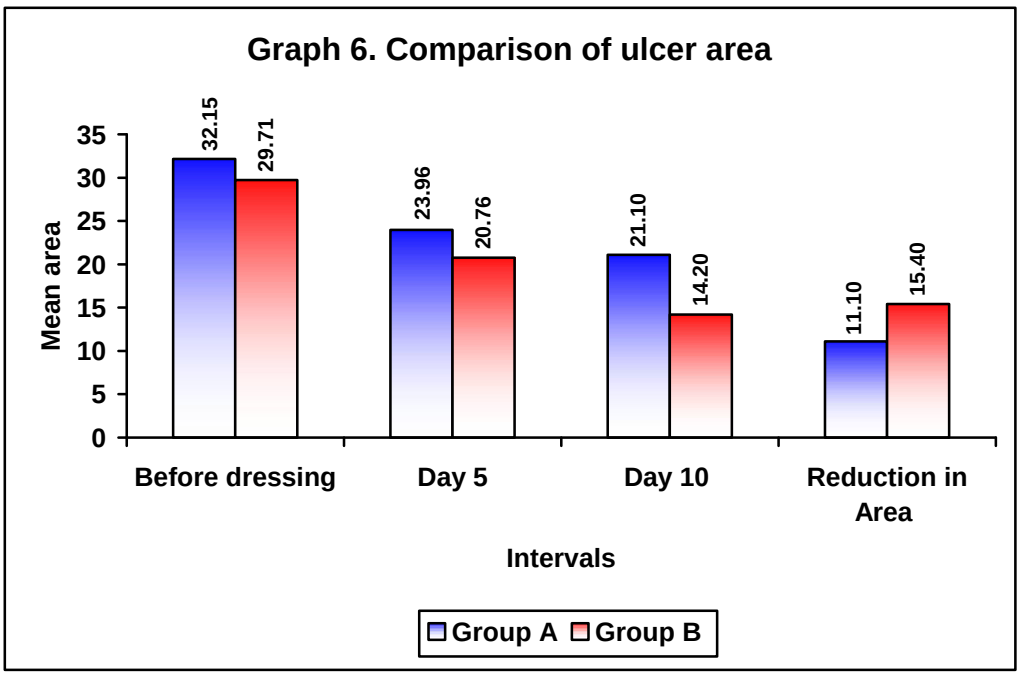
Table 9. Comparison of slough/necrotic tissue

Intervals	Slough/necrotic tissue	Group A (n=30)		Group B (n=30)		p value
		No	%	No	%	
Beginning	White/gray non-viable	1	3.33	4	13.33	**0.303**
	Non-adherent yellow	15	50.00	9	30.00	
	Loosely adherent yellow	9	30.00	10	33.33	
	Adherent, soft black eschar	4	13.33	6	20.00	
	Absent	1	3.33	0	0.00	
	W-S	0	0.00	1	3.33	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 10	White/gray non-viable	8	26.67	12	40.00	**0.115**
	Non-adherent yellow	16	53.33	16	53.33	
	Loosely adherent yellow	4	13.33	0	0.00	
	Adherent, soft black eschar	0	0.00	1	3.33	
	Absent	1	3.33	1	3.33	
	W-S	1	3.33	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 21	White/gray non-viable	13	43.33	23	76.67	**0.001**
	Non-adherent yellow	3	10.00	6	20.00	
	Loosely adherent yellow	14	46.67	1	3.33	
	Adherent, soft black eschar	0	0.00	0	0.00	
	Absent	0	0.00	0	0.00	
	W-S	0	0.00	0	0.00	
	Total	**30**	**100.00**	**30**	**100.00**	

In the present study most of the patients in the beginning had Non-adherent yellow slough/tissue in group A (50%) and group B (30%) (p=0.303). While on day 10, non-adherent yellow slough / necrotic tissue was noted in 53.33% of the patients each in group A and Group B (p=0.115). On day 21, most of the patients had white/gray non-viable slough/necrotic tissue in significantly high number of patients in group B (76.67%) compared to group A (43.33%) (p=0.001).

Table 10. Comparison of ulcer area

Intervals	Group A (n=30)		Group B (n=30)		t value	DF	P
	Mean	SD	Mean	SD			
Before dressing	32.15	25.63	29.71	24.34	0.708	58	0.583
Day 5	23.96	15.51	20.76	17.63	0.999	58	0.318
Day 10	21.10	13.84	14.20	10.65	1.942	58	0.052
Reduction in Area	11.10	16.24	15.40	16.63	1.493	58	0.149



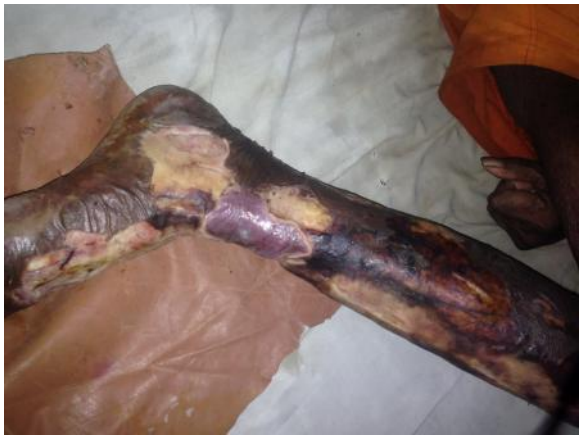
The comparison of ulcer area is as shown in table 10 and graph 6. It was observed that, wound area before dressing, on day five and day 10 was comparable. Even the reduction in ulcer area from day 21 to beginning of dressing was also comparable ($p > 0.050$).

Table 11. Comparison of wound culture

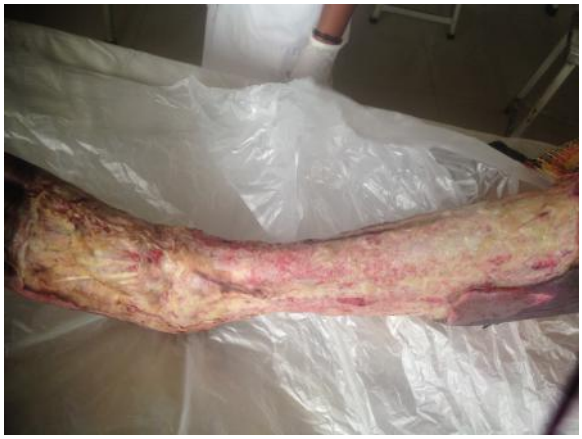
Variables	Findings	Group A (n=30)		Group B (n=30)		p value
		No	**%**	**No**	**%**	
Culture	Bacterioides fragilis	2	6.67	1	3.33	**0.886**
	E. coli	1	3.33	1	3.33	
	Pseudomonas	2	6.67	3	10.00	
	Staph Aureus	3	10.00	4	13.33	
	Negative	22	73.33	21	70.00	
	Total	**30**	**100.00**	**30**	**100.00**	
Day 10	Negative culture	30	100.00	29	96.67	**1.000**
	Bacterioides fragilis	0	0.00	1	3.33	
	Total	**30**	**100.00**	**30**	**100.00**	

In the present study most of the patients had negative wound culture at the beginning that is, 73.33% in group A and 70% in group B and the most common organism was staph aureus 10% in group A compared to 13.33% in group B (13.33%). On day 10 majority of the patients in group A (100%) and group B (96.67%) had negative culture (p=1.000).

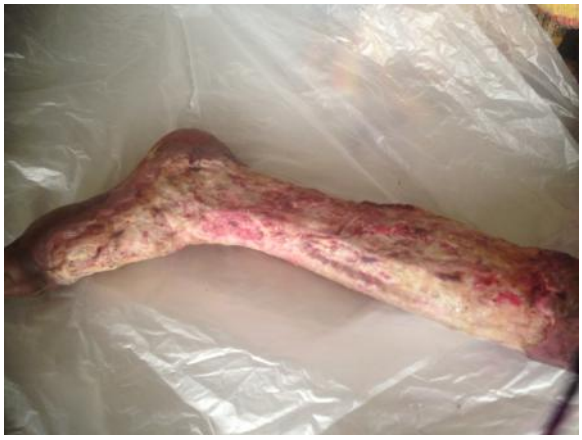
Photograph 2. Stages of wound healing using papain urea based preparation



Photograph 2a. Day 0

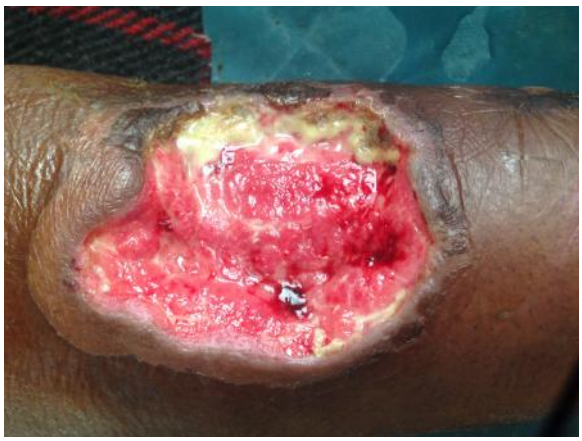


Photograph 2b. Day 10

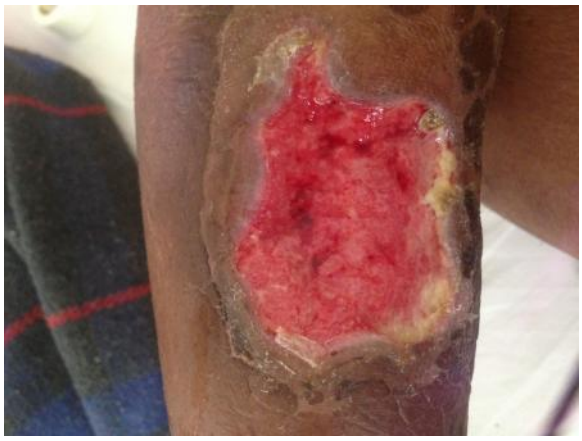


Photograph 2c. Day 21

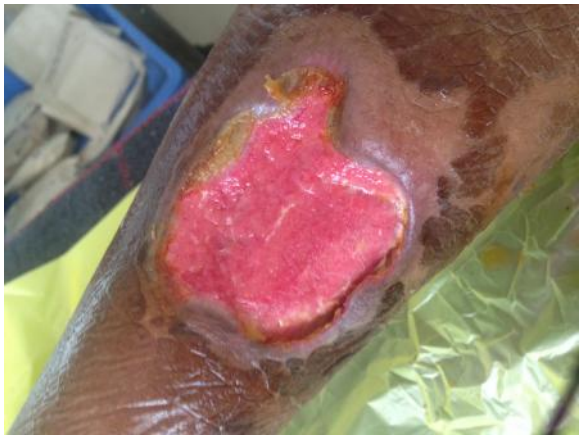
Photograph 2. Stages of wound healing using superoxidised solution



Photograph 3a. Day 0



Photograph 3b. Day 10



Photograph 3c. Day 21

DISCUSSION

The increasing prevalence of diabetes has resulted in concomitant illness. The critical effects of hyperglycemia include micro-vascular complications (nephropathy, neuropathy and retinopathy) and macro-vascular complications (coronary artery disease, stroke and peripheral arterial disease). Diabetes is a leading cause of non-traumatic lower extremity amputation, which is often preceded by a non-healing ulcer. The lifetime risk of foot ulceration in people with diabetes is 15%-20%. More than 15% of foot ulcers result in amputation of the foot or limb. Several other population-based studies indicate a 0.5%-3% annual collective incidence of diabetic foot ulcers. The prevalence of foot ulcers reported varies from 2% to 10%. Approximately 45%-60% of all diabetic foot ulcerations are purely neuropathic, whereas 45% have both neuropathic and ischemic components. It has been estimated that around 15%-27% patients with diabetes require lower limb amputations predominantly (50%) due to infection.[93]

Infection, ulceration or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular diseases in the lower limb (World Health Organization definition, 1995).

Debridement of necrotic tissue is an integral component in the treatment of chronic wounds as they do not heal in the presence of unviable tissue, debris, or critical colonization and may be contraindicated in arterial ulcers. Excision of necrotic tissue is necessary for wound healing. Calluses or thickened skin surrounding the ulcer need to be excised. Necrotic tissue removed on a regular basis can expedite the rate at which a wound heals and has been shown to increase the

probability of attaining full secondary closure.[96] This study compared the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of grade 2 diabetic foot ulcers, as assessed by the appearance of granulation tissue on the end of day 21.

The present randomized controlled trial was conducted in the Department of General Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi over a period, from January 2015 to December 2015. A total of 60 Diabetic Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers which are not healed and for which debridement is required for healing were enrolled. These patients were divided into two groups of 30 each that is Group A (Patients in this group underwent debridement with superoxidised solution) and Group B ((Patients in this group underwent debridement with papain-urea based preparation).

In the present study male outnumbered females. That is majority of the patients in group A (80%) and group B were males (86%). The male to female ratio was 4:1 in group A and 6.5:1 in group B. However the sex distribution pattern in group A and group B was comparable (p=0.488).

In this study 30% of the patients in group A and group B were aged between 41 to 50 years and 61 to 70 years in both the groups the mean age in group A was 61.56 ± 13.00 years compared to 58.53 ± 11.40 years. However the age distribution of the patients in group A and group B (p=0.362) as well as mean age in group A and group B were comparable (p=0.341). These findings suggest that, the

demographic characteristics of the study population were comparable in Group A and Group B.

In this study with regard to the diabetic characteristics, majority of the patients in group A (70%) and group B (76.67%) has type 2 diabetes mellitus (p=0.559). Most of the patients in group A (50%) and in group B (43.33%) presented with duration of >15 years (p-=0.817). The mean duration of diabetes in group A was slightly high (7.97± 5.65 years) compared to group B (7.00 ± 4.18 years) but this difference was statistically not significant (p=0.453). Pertaining to the medication, majority of the patients in both the groups that is, 80% in group A and 93.33% in group B were on insulin (p=0.129) Hence, the diabetic characteristics of the study population including type of diabetes, duration, and treatment modality did not differ in Group A and Group B.

In the present study ulcer characteristics were also comparable. It was observed that, most of the ulcers had traumatic mode of onset (56.67% in group A vs 60% in group B; p=0.684), duration of < 1 month (53.33% in group A and 63.33% in group B; p=0.792) and discharge was absent in most of the ulcers (83.33% in group A vs 93.33% in group B; p=0.212). The mean duration of under in group A was slightly high (4.68 ± 9.08 months) compared to group B (2.44 ± 4.48 months). But statistically this difference was not significant (p=0.232).

The above findings confirm that the study population in Group A and Group B did not differ significantly in terms of demographic, diabetic and ulcer characteristics ruling out the possible bias in the study results.

In the present study on day 10, wound observations revealed majority of the wounds with sloughy floor in most of the patients who belonged to group A and group B ((96.67% vs 93.33%; p=0.612) but on day 21, granulation was noted in significantly higher number of patients (73.33%) who belonged to group B compared to group A (46.67%) (p=0.035). These findings suggest that, debridement with papain-urea based preparation significantly influences granulation compared to debridement with superoxidised solution.

In this study at enrolment most of the patients had Non-adherent yellow slough/tissue in group A (50%) and group B (30%) (p=0.303). While on day 10, Non-adherent yellow slough / necrotic tissue was noted in 53.33% of the patients each in group A and Group B on day 10 (p=0.115). Whereas on day 21, most of the patients had in group B (76.67%) had White/gray non-viable slough/necrotic tissue compared to group A (43.33%) This difference was statistically significant (p=0.001) suggesting that, debridement with papain-urea based preparation significantly influences granulation as assessed by slough/necrotic tissue compared to debridement with superoxidised solution.

In this study comparison of ulcer area at enrolment (32.15 ± 25.63 vs 29.71 ±24.34 cm^2; p=0.583), on day five (23.96 ± 15.51 vs 20.76 ± 17.63 cm^2; p=0.318) and day 10 (21.10 ± 13.84 vs 14.20 ± 10.65 cm^2; p=0.052) was comparable. Even the reduction in wound area from beginning to day 21 of dressing was low in group B compared to group A same was not true statistically (11.10 ± 16.24 vs 15.40 ± 16.63 cm^2; p=0.149). These findings suggest that, debridement with papain-urea based preparation influences granulation compared to debridement with

superoxidised solution but statistically there both the modalities have similar outcomes.

In the present study most of the patients had negative wound culture at the beginning that is, 73.33% in group A and 70% in group B and the most common organism was staph aureus (10%) in group A and Bacterioides fragilis in group B (3.33%). However, On day 10, majority of the patients in group A (100%) and group B (96.67%) had negative culture (p=1.000). These findings suggest that, both the modalities that is, debridement with either papain-urea based preparation or with superoxidised solution is equally effective method in the prevention of infection.

Overall the present study showed that, debridement with papain-urea based preparation significantly influences granulation and thereby promotes early healing compared to debridement with superoxidised solution. Furthermore it is equally efficacious to that of superoxidised solution equally effective method in the prevention of infection. However we do not have adequate data to compare these findings with other studies. We hypothesize that, debridement with papain-urea based preparation might have multiple beneficial effects on wound bed preparation and healing. Through the removal of necrotic plug by the enzymatic action; The collagen bundles are being cut at the necrotic-viable tissue interphase; Rapid epithelialization that might occur either indirectly (as necrotic tissue is removed) or through the direct effect of collagenase on keratinocyte migration; The wound, now free of necrotic tissue, has good granulation tissue and is mostly epithelialized.[73]

It is reported that, papain/urea formulations have been demonstrated to have degrading effects on wound components, such as collagen, fibrin, and elastin both in vitro and clinically.[97]

A study showed that collagenase in vitro was capable of degrading both collagen and elastin, while papain/urea was effective for fibrin and collagen degradation.[98]

In another study by Alvarez et al.[99] (2000), papain-urea proved to be significantly more effective than collagenase for pressure ulcer debridement. Papain-urea also appeared to be more effective in promoting granulation tissue than collagenase. In two separate studies using different in vitro models for debridement.[98,100] It was shown that the combination of an enzyme (papain) with a mucolytic nonenzymatic agent (urea) was significantly more effective than enzymatic agents alone (collagenase or DNase/fibrinolysin).

The only RCT on papain reported more visible NTR and granulation tissue formation during weeks 2, 3, or 4 of debridement on pressure ulcers using papain combined with urea in a hydrophilic ointment vehicle compared to collagenase in petrolatum ointment in long-term care. There was no significant difference in healing rates (n = 26) (Ramundo, 2008). Papain-urea is in a white hydrophilic ointment, whereas collagenase debriding ointment has a petrolatum vehicle and is considerably more hydrophobic. Differences in the hydrophilic nature of the ointment vehicles between these two formulations may be of importance, since hydrophilic formulations have been shown to be more effective in releasing enzymes than hydrophobic formulations.[99] In this study efficacy of collagenase and papain-

urea was compared for ulcer debridement. It was found that there was no difference in reduction in ulcer size between the two groups. Papain-urea showed significant reduction in slough/necrotic tissue compared to collagenase .Granulation was better with papain-urea compared to collagenase. On clinical assessment of wound/ulcer significant improvement was noted in papain-urea group compared to collagenase.

Ramudo J. and Gray M.[101] to identify evidence related to the efficacy of enzymatic debriding agents collagenase and papainurea in the removal of necrotic tissue from the wound bed and its impact on wound healing concluded that, Enzymatic debriding agents are an effective alternative for removing necrotic material from pressure ulcers, leg ulcers, and partial-thickness wounds. They may be used to debride both adherent slough and eschar. Enzymatic agents may be used as the primary technique for debridement in certain cases, especially when alternative methods such as surgical or conservative sharp wound debridement (CSWD) are not feasible owing to bleeding disorders or other considerations. Many clinicians will select enzymes when CSWD is not an option. Clinical experience strongly suggests that combined therapy, such as initial surgical debridement followed by serial debridement using an enzymatic agent or enzymatic debridement along with serial CSWD, is effective for many patients with chronic, indolent, or nonhealing wounds.

Solange S. et al.[102] in 2010 reported that, Papain allows the effective removal of necrotic tissue in wounds by a type of enzymatic debridement. The objective of this work was to emphasize the effectiveness of the association of papain with urea in necrotic lesions. The case of a 56 year old patient is reported with an ulcerated lesion in the internal malleolar region of the left lower limb. The necrotic tissue was made enzymatic debridement using papain and urea and vitamin E supplement twice

daily. By the fourth day the debridement was complete and was changed to a bandage with carboxymethyl cellulose associated with pectin once daily. The association of papain with urea at 10% concentration proved to be efficient in the enzymatic debridement of a wound of the lower limb. This is another option of removing necrotic tissue when a selective process is desired.

The first studies on debridement using papain were published by Monetta L. et al.[95] who greatly contributed to this practice. Initially, different amounts of concentrated extracts, generally around 2.5%, were dissolved in saline solution. Currently the concentrations still vary but are normally around 1% to 3% depending on the experience of each professional.

In the USA, the use of an association of papain and urea has been reported in several studies.[95,103,104] Among the benefits of urea are its strong osmotic power which facilitates hydration of the wound, in particular the fibrous layer and its ability to supply sulfhydryl groups which facilitate the breakdown of collagen.[104]

Limited evidence suggests that a papain urea based ointment removes necrotic material from pressure ulcers more rapidly than collagenase ointment, but progress toward wound healing appears to be equivocal.[101]

More recently Hosmath V. et al.[97] in Bangalore compared the effectiveness of collagenase v/s papain– urea for debridement of chronic non-healing ulcers/wounds and to evaluate their role in promoting ulcer healing by granulation and reduction in ulcer/wound size. A comparative study of 100 patients was done at M.S. Ramaiah Hospitals in India from November 2007 to August 2009. Patients were selected, randomized, and divided into two groups consisting 50 patients each.

Group- 1 treated with collagenase and Group 2 with papain– urea. Patients were evaluated at 0, 1, 2, 3, and 4 weeks for reduction in ulcer size, granulation, discharge and over all response to treatment. The mean age was 42 +/- 15yrs. The co-morbidities were diabetes 28.4 %, hypertension in 21.1%, others 14.0%. Culture and sensitivity test reveals that most frequently grown organism was E. coli (13%) Staphyloccus aureus (9%) and samples with no growth was 64%. In papain-urea group, ulcer was reduced from 24.8 sq. cms to 11.9 sq. cms and collagenase group 23.1 sq. cms to 9.7 sq. cms. There was significant reduction in slough and necrotic tissue i.e. in papain-urea group 22.54 sq. cms to 5.07 sq. cms and collagenase group 21.76 sq. cms to 6.12 sq. cms. Significant amount of increase in granulation tissue in papain-urea group i.e., 2.4 sq. cms to 6.82 sq. cms and collagenase group 1.4 sq. cms to 3.8 sq. cms was observed. But Papain-urea group showed better response in 2nd, 3rd, 4th weeks compared to collagenase (p value <0.05) and significant improvement in 28% in papain-urea, 12% in collagenase group. Mean follow-up period was 7.28- 8.14wks. Authors commendted that, Papain-urea and collagenase have shown proven efficacy in bringing out enzymatic wound debridement. Papain-urea is a better enzymatic debriding agent promotes faster granulation compared to collagenase a finding which was in agreement with the present study.

The findings this study were consistent with observations made by Alvarez et al.[99] who compared Collagenase vs papain urea ointment for adults with pressure ulcers, the mean age for collagenase was 76 while it was 74 for papain urea ointment group. Authors concluded that, Wounds debrided with papain-urea had more rapid removal of necrotic tissue from the wound bed but change in wound size did not differ between groups.

In contrast to the findings of this study, Anand A. et al.[105], compared efficacy of SOS versus Povididine iodine (PI) in post C-section wounds, showed that 88% had granulation by day 5 in SOS group compared to 80% in PI group and by day 10 there was granulation in all patients. By day 5, 4% in SOS group had erythema at surgical wound compared to 12% in PI group. Similarly Wolvos TA55 concluded that Superoxidized solution could be used to treat a variety of wounds from simple to extremely complex. It can be used as the wound irrigation solution at simple dressing changes, and it can serve as the solution to moisten the gauze used to dress the wound.

Overll this study shows more favourable results with debridement with papain-urea based preparation as compared to debridement with superoxidised solution in healing of grade 2 diabetic foot ulcers. However, the limitations of the study were smaller sample size. Further multicentric studies with large sample size are required to confirm these observations.

CONCLUSION

Based on the findings of this study, it may be concluded that, debridement with papain-urea based preparation significantly influences granulation and thereby promotes early healing compared to debridement with superoxidised solution. Furthermore it is equally efficacious to that of superoxidised solution equally effective method in the prevention of infection. Hence Papain-urea is a better enzymatic debriding agent promotes faster granulation compared to superoxidised solution.

SUMMARY

There has always been a search for an ideal antiseptic that is rapidly lethal to all forms of bacteria and their spores, capable of bactericidal property for a prolonged period with no ill effect on host tissues. It is reported that, enzymatic ulcer debridement is effective in debridement of chronic nonhealing ulcers and also decrease exudates, bacterial burden and promote ulcer healing. This study was aimed to compare the effectiveness of Papainurea based preparation vs Superoxidised solution in debridement of grade 2 diabetic foot ulcers, as assessed by the appearance of granulation tissue on the end of day 21.

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 2015 to December 2015. A total of 60 Diabetic Patients taking insulin or oral hyperglycaemic and suffering from diabetic foot ulcers which are not healed, over a period of > 3 weeks and for which debridement is required for healing Patients, were enrolled. These patients were divided into two groups of 30 each that is First group (Group A) with superoxidised solution and Second group (Group B) with papain-urea based preparation.

In the present study 80% of the patients in group A and 86% of the patients in group B were males. (p=0.488) The mean age in group A was 61.56 ± 13.00 years compared to 58.53 ± 11.40 years (p=0.341). It was observed that, majority of the patients in group A (70%) and group B (76.67%) has type 2 diabetes mellitus (p=0.559). The mean duration of diabetes in group A was 7.97± 5.65 years compared to 7.00 ± 4.18 years in group B (p=0.453). Most of the ulcers had

traumatic mode of onset (56.67% in group A vs 60% in group B; p=0.684). The mean duration of ulcer in group A was 4.68 ± 9.08 months compared to 2.44 ± 4.48 months group B (p=0.232). On day 10 wound observations revealed majority of the wounds with sloughy floor in group A (96.67%) and group B (93.33%) (p=0.612). While on day 21 significantly higher number of patients (73.33%) in group B had granulation compared to group A (46.67%) (p=0.035). Most of the patients had Non-adherent yellow slough/tissue in group A (50%) and group B (30%) (p=0.303). while on day 10, Non-adherent yellow slough / necrotic tissue was noted in 53.33% of the patients each in group A and Group B on day 10 (p=0.115). On day 21, most of the patients had White/gray non-viable slough / necrotic tissue in significantly high number of patients in group B (43.33%) compared to group A (43.33%) (p=0.001). It was observed that, wound area before dressing, on day five and day 10 was comparable. Even the reduction in wound area from day 21 to beginning of dressing was also comparable (p> 0.050). Most of the patients had negative wound culture at enrollment that is, 73.33% in group A and 70% in group B and the most common organism was staph aureus (10%) in group A and Bacterioides fragilis in group B (3.33%). On day 10 majority of the patients in group A (100%) and group B (96.67%) had negative culture (p=1.000).

Papain-urea seems to be a better enzymatic debriding agent promotes faster granulation compared to superoxidised solution.

BIBLIOGRAPHY

1. IDF Diabetes Atlas. 6th ed., Poster Update. Belgium: International Diabetes Federation; 2014.

2. Joshi SR, Parikh RM. India - diabetes capital of the world: now heading towards hypertension. J Assoc Physicians India 2007;55:323-4.

3. Kumar A, Goel MK, Jain RB, Khanna P, Chaudhary V. India towards diabetes control: Key issues. Australas Med J 2013;6(10):524-31.

4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes-estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(3):1047-53.

5. Whiting Dr, Guariguata L, Weil C, Shawj. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011;94:311-21.

6. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7(1):45-8.

7. Fauci AS, Kasper DS, Longo DL, Braunwald E, Hauser SL, Jameson JL, et al. Harrison's principles of internal medicine. United States; McGraw Hill: 2008.

8. Thomson FJ, et al. A team approach to diabetic foot care: the Manchester experience. Foot 1991;1:75-82.

9. Williams R, Airey M. The size of the problem: economic aspects of foot problems in diabetes. In: Boulton AJM, Connor H, Cavanagh PR, eds. The Foot in Diabetes, 3rd ed., Chichester: Wiley; 2000. p. 3-17.

10. Janka HU, StandI E, Mehnert H. Peripheral vascular disease in diabetes mellitus and its relation to cardiovascular risk factor: screening with Doppler ultrasonic technique. Diabetes Care 1980;3:207.

11. Palumbo PJ, Melton LJ. Peripheral vascular disease and diabetes In: Diabetes in America. Harris MI, Hamman RF eds., NIH 1985; Publ No.85 – 1468. Washington: US Government Printing Office; 1985. p. XVI-21.

12. Pendsey SP. Understanding diabetic foot. Int J Diabetes Dev Ctries 2010; 30(2):75–9.

13. Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wound dressings in diabetic foot disease. Clin Infect Dis 2004;39(2):S100-3.

14. Edmonds M, Foster A. The use of antibiotics in the diabetic foot. Am J Surg 2004;187(5A):25S-8.

15. Kapur V, Marwaha AK. Evaluation of Effect and Comparison of Superoxidised Solution (Oxum) V/S Povidone Iodine (Betadine). Indian J Surg 2011;73(1):48–53.

16. Sekiya S, Ohmori K, Harii K. Treatment of infectious skin defects or ulcers with electrolyzed strong acid aqueos solution. Artif Organs 1997;21:32-8.

17. Tanaka H, Hirakata Y, Kaku M, Yashida R, Takemura H. Antimicrobial activity of duper oxidized water. J Hosp Infect 1996;34:43-9.

18. Sibbald RG, Williamson D, Orsted HL, Campbell K, Keast D, Krasner D, Sibbald D. Preparing the wound bed--debridement, bacterial balance, and moisture balance. Ostomy Wound Manage. 2000;46:14-22,24-8,30-5.

19. Landis S, Ryan S, Woo K, Sibbald RG. Infections in chronic wounds. 4th ed. HMP Communications: 2007. p. 299-321.

20. Ayello EA, Cuddigan JE. Debridement: controlling the necrotic/cellular burden. Adv Skin Wound Care 2004;17(2):66–75.

21. McCallon SK, Weir D, Lantis, JC, Optimizing Wound Bed Preparation With Collagenase Enzymatic Debridement. J Am Coll Clin Wound Spec. 2014;6(1-2):14-23.

22. Miller JM et al and Howard F The interaction of papain, urea, and water-soluble chlorophyll in a proteolytic ointment for infected wounds. Surgery 1958;43:939-94.

23. Sekiya S,Ohmori K, Harii K. Treatment of infectious skin defects or ulcers with electrolyzed strong acid aqueos solution. Artif Organs 1997;21:32-8.

24. Tanaka H, Hirakata Y, Kaku M,Takemura H Antimicrobial activity of duper oxidized water. J Hosp Infect 1996;34:43-9.

25. Pelle MT, Miller OF. Debridement of necrotic eschar with 40% urea paste speeds healing of residual limbs and avoids further surgery. Arch Dermatol 2001;137:1288-90.

26. Pontiroli AE, Calderara A, Pozza G. Secondary failure of oral hypoglycaemic agents: Frequency, possible causes, and management. Diabetes Metab Rev 1994;10:31-43.

27. Houssay BA, Biasotti A. The hypothesis, carbohydrate metabolism and diabetes. Endocrinology 1931;15:511-23.

28. Leutholtz BC, Ripoll I. Exercise and disease management. 2nd ed., Boca Raton: CRC Press; 2011.

29. Hemsworth HP. Diabetes its differentiation into insulin-sensitive and insulin-insensitive types. The Lancet 1936;1:127-30.

30. Swain RP, Subudhi BB, Mahapatra AK, Bolapreddi V. Bridging Between Disease, Prevalence and Treatment of Diabetes Mellitus: A Review. Int J Pharm Tech Res 2015;7(2):212-28.

31. Kopelman PG, Hitman GA. Naturally occurring antihyper glycemic and antidyslipedimic agents. The Lancet 1998;5:352.

32. Shi Y, Frank B. The global implications of diabetes and cancer. The Lancet 1947;9933:383.

33. William's text book of endocrinology. 12th ed., Philadelphia: Elsevier; 1996.

34. Vos T, Flaxman AD, Nghavi M, Lozano R, Michaud C, Ezzati M, et al. A systemic analysis for the global burden of disease study, The Lancet 2010;380 (9859):2163.

35. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLOS Med. 2006;3(11):442.

36. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice. 2010;87:4-14.

37. Diabetes Atlas. 6th ed., International Brusels: Diabetes Federation; 2013.

38. IDF Diabetes Atlas. 4th ed., Brusels: International Diabetes Federation; 2009.

39. Patil RS, Gothankar JS. Prevalence of Type-2 Diabetes Mellitus and Associated Risk Factors in an Urban Slum of Pune City, India. Natl J Med Res 2013;3(4):346-9.

40. Mohan V, Pradeepa R. Epidemiology of diabetes in different regions of India. Health Administrator 2009;22:1–18.

41. Rao CR, Kamath VG, Avinash Shetty, Asha Kamat. A study on the prevalence of type 2 diabetes in coastal Karnataka. Int J Diabetes Dev Ctries 2010;30(2):80-5

42. World Health organization. Global status report on noncommunicable diseases. 2010. Available from:http://www.who.int/nmh/publications /ncd_report2010/en/ Access Date 18.05.2015.

43. Fowler MJ. Microvascular and micorvascular complications of diabetes. Clin Diab 2008;26(2):77-82.

44. Boulton M, Marshall J. He-Ne laser stimulation of human fibroblast proliferation & attachment in vitro. Lasers in Life Sci 1986;1:125-34.

45. Clement S, Braithwaite SS, Magee MF, Ahmann A, Smith EP, Schafer RG, et al. Management of diabetes and hyperglycemia in hospitals. Diabetes Care 2004;27:553.

46. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: An update. Ann Intern Med 2002;137:25.

47. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes prevention program research group: Reduction in the incidence of type-2 diabetes with lifestyle intervention of metformin. N Engl J Med 2002;346:393-403.

48. Saltiel AR, Kahn CR. Insulin signaling and the regulation of glucose and lipid metabolism. Nature 2001;414:799.

49. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group Epidemiology of the diabetes interventions and complications research group: Effect of intensive therapy on the microvascular complications of type-I Diabetes mellitus. JAMA 2002;287:2563-9.

50. UK Prospective Diabetes Study (UKPDS) Group (UKPDS 33). Intensive blood-glucose control with sulphonylureas or insulin compared with

conventional treatment and risk of complications in patients with type-2 diabetes. Lancet 1998;352:837-53.

51. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes 2015;6(1):37-53.

52. Fryberg RG. Diabetic foot ulcers:pathogenesis and management. Am Fam Phys 2002;66(9):1655-62.

53. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Plast Reconstr Surg 2006;117(7 Suppl):212S-38S.

54. The Average Age of Onset of Diabetes Among Indians is a Decade Earlier Than Other Races. Available on http://www.expresshealthcare.in/201110/ diabeteswatch05.shtml. Accessed date: 13.01.2012

55. Boulton AJ. Pressure and the diabetic foot: clinical science and offloading techniques. Am J Surg 2004;187(5A):17S-24S.

56. Arora S, Pomposelli F, LoGerfo FW, Veves A. Cutaneous microcirculation in the neuropathic diabetic foot improves significantly but not completely after successful lower extremity revascularization. J Vasc Surg 2002;35(3): 501-5.

57. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763-71.

58. Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, Landsman AS, Lavery LA, Moore JC, Schuberth JM, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision) J Foot Ankle Surg 2006;45:S1–66.

59. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet 2005;366:1719-24.

60. Nielson DL, Ali Y, Diabetic Foot Infections J Am Podiatric Med Assoc 2009;99 (5):454-8.

61. Tomic-Canic M, Brem H. Gene array technology and pathogenesis of chronic wounds. Am J Surg 2004;188(1A Suppl):67-72.

62. Frykberg RG. Diabetic foot ulcers:current concepts. J Foot Ankle Surg 1998;37:440-6.

63. Abergel RP, Mecker CA, Lam TS, Dwyer RM, Lesavoy MA. Uitto J. Control of connective tissue metabolism by lasers: Recent developments and future prospects. J Am Acad Dermatol 1984;11:1142-50.

64. Yu W, Naim JO, Lanzafame RJ. The effects of photo-irradiation on the secretion of TGF and PDGF from fibroblasts in vitro. Lasers Surg Med Suppl 1994;6:8.

65. Effects of 810 nm laser irradiation on in vitro growth of bacteria:Comparison of continuous wave and frequency modulated light. Lasers Surg Med 2002;31(5):343-51.

66. Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D. Systematic reviews of wound care management: Dressings and topical agents used in the healing of chronic wounds. Health Technol Assess 1999;3(17 Pt 2):1-35.

67. Dyson M, Young S, Pendle CL, Webster DF, Lang SM. Comparison of the effects of moist and dry conditions on dermal repair. J Invest Dermatol 1988;91(5):434–9.

68. Fivenson DP, Faria DT, Nickoloff BJ, Poverini PJ, Kunkel S, Burdick M, et al. Chemokine and inflammatory cytokine changes during chronic wound healing. Wound Repair Regen 1997;5:310–22.

69. American Diabetes Association. Clinical Practice recommendations. Diabetes Care 2001;24 (Suppl 1):S1-145.

70. European Wound Management Association Document: Debridement. Available from: URL: http://ewma.org/english/ewma-news/show/ article/ewma-document-on- debridem.... Published Jan. 8, 2013. Acces Date: 9.07.2016.

71. Belken T, Mozen N. Current And Emerging Modalities In Wound Debridement. Podiatry Today 2013;26(8): Available from: URL: http://www.podiatrytoday.com/current-and-emerging-modalities-wound-debridement Aceess date: 21.06.2016.

72. Percival SL, Bowler P, Woods EJ. Assessing the effect of antimicrobial wound dressings on biofilms. Wound Repair Regen. 2008; 16(1):52-57.

73. Falanga V, Harding KG. The Clinical Relevance of Wound Bed Preparation. New York: Springer Verlag; 2002.

74. Ayello E, Cuddigan J, Kerstein MD. Skip the knife: debriding wounds ithout surgery. *Nursing.* 2002;32(9):58-63.

75. Steed DL, Donohoe D, Webster MW, Lindsley L. Effect of extensive debridement and treatment on healing of diabetic foot ulcers. Diabetic Ulcer Study Group. J Am Coll Surg 1996;183(1):61-4.

76. Williams D, Enoch S, Miller D, et al. Effect of sharp debridement using curette on recalcitrant nonhealing venous leg ulcers: a concurrently controlled, prospective cohort study. Wound Repair Regen 2005;13(2): 131-7.

77. Gray D, Acton C, Chadwick P, et al. Consensus guidance for the use of debridement techniques in the UK. Wounds UK 2011;7(1):77-84.

78. Kavos SJ, Liedl DL, Boon AJ, Miller JL, Hobbs JA, Andrews KL.. Expedited wound healing with noncontact, low-frequency ultrasound therapy in chronic wounds: a retrospective analysis. *Adv Skin Wound Care.* 2008; 21(9):416-23.

79. Westerhof W. Future prospects of proteolytic enzymes and wound healing. In: Westerhof W, Vanscheidt W (eds). Proteolytic Enzymes and Wound Healing. New York, NY: Springer-Verlag and Co. 1994. p. 99-102.

80. Berger MM. Enzyme debriding preparations. Ost/Wound Manag 1993;39:61-6.

81. Rodeheaver G, Marsh BS, Edgerton MT, Edlich RF. Proteolytic enzymes as adjuncts to antimicrobial prophylaxis in contaminated wounds. Am J Surg 1975;129:537-42.

82. Smith B. Expression and regulation of the collagen family in skin. In: Falanga V (ed). Cutaneous Wound Healing. London: Martin Dunitz Publishers, 2001:57-80.

83. Miller JM, Howard F. The interaction of papain, urea, and water-soluble chlorophyll in a proteolytic ointment for infected wounds. Surgery 1958;43:939-48.

84. Silverstein P, Ruzicka FJ, Helmkamp GM, et al. In-vitro evaluations of enzymatic debridement of burn eschar. Surgery 1973;73:15-22.

85. Falanga V. Wound Bed Preparation and the Role of Enzymes: A Case for Multiple Actions of Therapeutic Agents. Wounds 2002;14(2)

86. Wrigth JB, Shi L. Accuzyme® Papain-Urea Debriding Ointment: A Historical Review. Wounds 2003;15(5):133-42.

87. Paola LD, Brocco E, Senesi A, Merico M, De Vido D, Assaloni R, et al. Super-Oxidized Solution (SOS) Therapy for Infected Diabetic Foot Ulcers. Wounds 2006;18(9):262-70.

88. Chittoria RK, Yootla M, Chandra LM, Rao DS Venkat Raman S. The role of super oxidized solution in the management of diabetic foot ulcer: Our experience. Available from: URL : http://www.nmcth.edu/images/

gallery/Short%20Communication/iPvidRavi%20Kumar%20Chittoria.pdf 18.069.2016

89. Nelson D. Newer technologies for endoscope disinfection: Electrolyzed acid water and disposable- component endoscope system. Gastrointestinal Endosc Clin N Am 2000; 10: 319-28.

90. Gutierrez Andres A. The science behind stable super oxidized water exploring the various applications of super-oxidized solutions in clinical experience with a new and stable superoxidized water in wound treatment, advanced wound care with stable, superoxidized water. Supplement to January 2006 Wound (A compendium of Clinical Research and Practice) Page 7–10.

91. Goretti C, Mazzurco S, Nobili LA, Macchiarini S, Tedeschi A, Palumbo F, et al. linical outcomes of wide postsurgical lesions in the infected diabetic foot managed with 2 different local treatment regimes compared using a quasi-experimental study design: a preliminary communication. Int J Low Extrem Wounds. 2007 Mar;6(1):22-7.

92. Anand A, Comparative Efficacy and Tolerability of Oxum against Povidone Iodine Topical Application in the Post-caesarean Section Wound Management. Indian Medical Gazette 2007;498-505.

93. Tom WA. A look at how combination therapy can optimize wound healing in Clinical Experience With A New And Stable Super-Oxidized Water In Wound Treatment, Advanced Wound Care with Stable, Superoxidized Water.

Wounds 2006; (A Compendium Of Clinical Research And Practice) Page 11-3.

94. Pandey PK, Koushariya M, Shukla S, Das S. Outcomes of superoxide solution dressings in surgical wounds: a randomized case control trial. Int J Biol Med Res 2011; 2(4): 965-8

95. Monetta L, et al, Uso da papaína nos curativos feitos pela enfermagem. Rev. Bras. Enf Brasília 1988; 40(1):16-66.

96. Kavitha KV, Tiwari S, Bharat Purandare VB, Khedkarr S, Bhosale SS, Unnikrishnan AG. Choice of wound care in diabetic foot ulcer: A practical approach. World J Diabetes 2014;5(4):546-6.

97. Hosamath V, Sreekar AP, Pandey V, Kamble P. Comparative study of collagenase and papain-urea based preparations in the management of chronic nonhealing limb ulcers Indian J Sci and Technol 2011; 4(9):1096-100.

98. Hobson D, Lira L, Nijeha F. Evaluation of the effects of formulation factors on the action of wound debriding agents in vitro. Abstract presented at the 30th Ann. Conf. of the Wound Ostomy and Continence Nursing Soc. in Salt Lake City, Utah, 1998;13-7.

99. Alvarez OM, Fernandez-Obregon A, Rogers RS, Bergamo L, Masso J, Black M. Chemical debridement of pressure ulcers: A prospective, randomized comparative trial of collagenase and papain/urea formulations. Wounds 2000;12 (2):15-25.

100. Levenson SM, Gruber DK, Gruber C Chemical debridement of burns: Mercaptans. J. Trauma. 1981;21:632-44.

101. Ramundo J and Gray M. Enzymatic wound debridement. J. Wound Ostomy Continence Nurs 2008;35(3):273–280.

102. Silveira, Solange; Dias Guimarães, Tânia Papain Associated with Urea in the Debridement of Necrotic Wounds J Phlebology & Lymphol 2010;3:6

103. Masini E, Calamo MA,Uma forma de tratamento de lesões cutâneas com papaína e sacarose. Ver Bras Clin Terap 1986;15:2435-48.

104. Miranda Altamirano A, Medina Preciado D, Chavez Velarde T, et al, Treatment of 2nd and 3rd Degree Burns in 64 Pediatric Patients Without Routine Antibiotics using New “Super-oxidized Solution Technology” Texas Surgical Society Congress. San Antonio, Tx. 1st–3rd April, 2005 and European Burns Association Meeting 2005. Estoril Portugal 2005;

105. Anand, A. Comparative Efficacy and Tolerability of Oxum against Povidone Iodine Topical Application in the Post-caesarean Section Wound Management." Indian Med Gazette 2007;498-505.

ANNEXURE I – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY.

Mr./Mrs./Miss.……..we are requesting you to enroll yourself in study titled A **RANDOMISED CONTROL TRIAL TO COMPARE OF PAPAINUREA BASED PREPARATION VS SUPEROXIDISED SOLUTION IN THE MANAGEMENT OF GRADE 2 DIABETIC FOOT ULCER,AT KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI FOR ONE YEAR"** by Dr. **** **** **** , Post Graduate in M.S. GENERAL SURGERY under the guidance of DR. *** ***** M.S., Professor & Head of Department of General surgery, Jawaharlal Nehru Medical College, Belagavi, under KLE university, Belagavi.

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J. N. Medical College and KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI. If you decide to participate you are free to withdraw at any time.

Purpose of the study

"The purpose of the study is to find out the effectiveness of Papain-urea based preparation in diabetic foot ulcer debridement when compared with Superoxidised solutions"

Procedure involved

Methodology

The patient will be randomly divided into 2 groups. **(By envelope method)**

First group with superoxidised sol.

Second group with papain-urea based preparations

Method of application

Application of ointment was done once daily in the following manner:

Step 1: Prior to application, the lesion was cleaned of debris and digested material by gently rubbing with gauze pad by normal saline.

Step 2: Whenever infection is present, an appropriate topical antibiotic powder should be applied to the lesion prior to the application of Ointment.

Step 3: Ointment was applied directly to deep lesions with a wooden tongue depressor or spatula. For shallow lesions, Ointment was applied on sterile gauze pad, which was then applied to the wound and properly secured.

Step 4: All excess ointment was removed each time dressing was change.

Use of ointment should be **terminated** when debridement of necrotic tissue is complete and granulation tissue is well established or for a maximum period of 3 weeks or 21 days.

- Same antibiotic will be used for both the groups.

Assessments

Assessments are to be done pre-debridement but after cleansing the wound. Evaluators should note the exudate type and amount on removal of dressings. Whenever possible, the time since the last dressing change should be consistent from one assessment to the next.

- Assessment will mainly be done by comparing slough/non viable tissue, discharge, odour, noting granulation tissue.
- Size—Measure length as the longest diameter; width is perpendicular to length. Avoid diagonals. Calculate wound area as length by width. Write this in space provided and select appropriate response category.

Risk

A small percentage of patients may experience a transient "burning" sensation upon application of the spray. More frequent dressing changes will alleviate such discomfort until amount of exudates decreases.

Papain-urea is contraindicated in patients who have shown sensitivity to papain or any other components of its preparation.

There is no increased risk involved in becoming a part of the study and the complications are those which are normally anticipated.

Benefits

The combination of papain and urea is probably twice as effective in protein digestion as papain alone. An advantage of the papainurea combination may be nonspecific bulk debridement within a broad pH range (3.0–12.0). The papain-urea preparations have been used clinically for decades, especially in pressure ulcers.

The study will help us to compare the efficacy of Papainurea based preparation vs. superoxidised sol. in the management of grade 2 diabetic foot ulcer.

Voluntary participation/withdrawal

Taking part in the study is voluntary. You may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management

Privacy and confidentiality

The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.

2. If required by law

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential

Financial incentive for participation

No financial incentives are being offered to enrolled patients. It is purely done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury related to the study, treatment will be made available through KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI. There is no compensation or payment for such medical treatment by law. If you are injured you may contact Dr. **** ***** ***** *****, at Department of General Surgery, KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI.

Questions

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. **** ***** ***** **** , Department of General Surgery, KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI. Phone number: *** ***** or Dr. ***** ***** . Professor in the Department of General Surgery, KLE'S DR. PRABHAKAR KORE HOSPITAL & MRC, BELAGAVI.

If you have any queries about your rights as a subject, you may call Dr. Ganga Pilli, Professor, Department of Pathology and Chairman J. N. Medical College Institutional Ethical Committee for Human Subjects Research, Phone number: ***** ***** or extension **** at Jawaharlal Nehru Medical College, Belagavi**.**

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

I, Mr. /Mrs. _____

voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having been explained to me in my vernacular language including risks and the benefits and having all queries cleared.

Subject Name : _____

Signature of the participant: _____

Or Left thumb print: _____

Witness name: _____

Signature: _____

Investigator's name: _____

Place: _____

Date: _____

Signature of the investigator: _____

ANNEXURE II – PROFORMA

1. PATIENT IDENFICIATION DATA

Group: Case no. :

IP/OPD No: Date of Admission:

Name: Date of Surgery:

Sex: Date of Discharged:

Occupation:

Address:

2. Chief complaints

3. Medical history

Peripheral neuropathy : ( )

Nephropathy : ( )

Retinopathy : ( )

Peripheral vascular disease : ( )

Cardiovascular disease : ( )

4. Diabetic status

Type : Duration :

Medication :

Oral Hypoglycemic : ( )

Insulin : ( )

5. Ulcer detail

1. <u>Mode of onset</u>

1-Traumatic 2-Spontaneous

3-Pressure 4-Others

2. Duration

3. Progress

6. Wound observations

	Before dressing Day 0	Day 5	Day 10
1. Site			
2. Size (greatest dimension) 1- <5cms. 2- 6-10cms. 3- 11-15cms.			
3. Shape 1- Oval 2- Circular 3- Irregular			
4. Edge 1.Indistinct, diffuse = unable to clearly distinguish wound outline. 2.Attached = even or flush with wound base, no sides or walls present; flat. 3.Not attached = sides or walls are present; floor or base of wound is deeper than edge. 4.Rolled under, thickened = soft to firm and flexible to touch 5.Hyperkeratosis = callous-like tissue formation around wound and at edges 6.Fibrotic, scarred = hard, rigid to touch			
5. Margin			
6. Floor			
7. Base			
8. Discharge 1.Bloody = thin, bright red 2.Serosanguineous = thin, watery, pale red to pink 3.Serous = thin, water, clear 4.Purulent = thin or thick, opaque tan to yellow 5.Foul purulent = thick, opaque yellow to green with offensive odor			
9. Surrounding Skin			
10. Slough /necrotic tissue 1.White/gray non-viable = may appear prior to wound opening; skin surface is white or gray. 2.Non-adherent yellow slough = thin, mucinous substance; scattered throughout wound bed; easily seperated from wound tissue. 3.Loosely adherent yellow slough = thick, stringy clumps of debris; attached to wound tissue. 4.Adherent, soft black eschar = soggy tissue; strongly attached to tissue in center or base of wound. 5.Firmly adherent, hard black = firm, crusty tissue; strongly attached to wound base and edges (like a hard scab). 11. Area of the ulcer			

7. Vascular examination

	Right	Left
Popliteal artery		
Ant. Tibial artery		
Post Tibial artery		
Dorsalis Pedis artery		

1) Present

2) Absent

8. Any foot deformity present

Toe deformity:

Charcot's foot:

Foot drop :

1-Present

2-Absent

9. If debridement has been done

Specify, Date :

Side :

Type of anaesthesia :

No of debridements :

10. Investigations

Complete blood count: ( ) Haemoglobin : ( )

Total leukocyte count : ( ) Direct count :(N - , L- , M-, and E-)

Fasting blood sugar: ( ) Date Time

Blood Urea ( )

Serium Creatinine ( )

Urine

Routine

Microscopy

X-ray

AP view

Lat. View

Culture/ sensitivity

Before dressing at Day 0:

Day 14:

Colour doppler

ANNEXURE III – KEY TO MASTER CHART

A	-	Absent
A. block	-	Ankle block
Ant.	-	Anterior
BDS	-	Blackish discolouration
BF	-	Bacteroides fragilis
CVD	-	Cardiovascular disease
D-P	-	Dark pigmentation
E. coli	-	Escerachia coli
F	-	Female
g - t	-	Granulation tissue
H.W	-	House wife
Lt foot	-	Left foot
M	-	Male
M.S	-	Minimal slough
N	-	Normal
N.A	-	Not applicable
No.	-	Number
NWD	-	Not well defined
O-H-A	-	Oral hypoglycaemic agent
P	-	Present
pig +	-	Pigmentation
PVD	-	Peripheral vascular disease
Rt foot	-	Right foot

S	-	Spontaneous
S. Aureus	-	Staph aureus
SA	-	Spinal anaesthesia
ST	-	Slogh tissue
S-T	-	Slough tissue
T	-	Traumatic
TE	-	Tendon exposed
WD	-	Well defined
W-S	-	White slough