“A RANDOMISED CONTROL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH SUPEROXIDISED SOLUTION VERSUS POVIDINE IODINE IN MANAGEMENT OF INFECTED DIABETIC ULCERS”

REG.NO. BH0111008

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. S.
in
GENERAL SURGERY

DEPARTMENT OF SURGERY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"A RANDOMISED CONTROL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH SUPEROXIDISED SOLUTION VERSUS POVIDINE IODINE IN MANAGEMENT OF INFECTED DIABETIC ULCERS"** is a bonafide research work done by **THE CANDIDATE REG. NO. BH0111008**.

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LIST OF ABBREVIATIONS USED

AP	-	Antero-posterior
ClO2	-	Chlorine dioxide
DM	-	Diabetes mellitus
E. coli	-	Escherichia coli
FAC	-	Free available chlorine
g	-	Gram
H_2O	-	Oxidized solution
H_2O_2	-	Hydrogen peroxide
HOCI	-	Hypochlorous Acid
i.e.	-	That is
ICMR	-	Indian Council of Medical Research
mm	-	Millimeter
MRI	-	Magnetic resonance imaging
MRSA	-	Methicillin-resistant Staphylococcus aureus
n	-	Total number
Na_2CO_3	-	Sodium Carbonate
NaCl	-	Sodium chloride
NaOCI	-	Sodium hypochlorite
NaOH	-	Sodium hydroxide
O_3	-	Ozone
p	-	Probability
PI	-	Povidine iodine
RCTs	-	Randomized controlled trials
SD	-	Standard déviation
VRE	-	Vancomycin-resistant enterococci

ABSTRACT

Background and Objectives

Diabetic foot ulcer is a challenging problem to every clinician in day to day practice. Superoxidised Solution is a newer concept in the wound management. The present study was aimed to compare the efficacy of dressings with superoxidised solution versus povidine iodine in the management of infected diabetic ulcers.

Methodology

This one year randomized controlled trial was conducted on a total of 60 patients presenting with infected diabetic ulcers from January 2012 to December 2012 in the Department of General Surgery at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. The patients were divided into two groups of 30 each based on computer generated randomization that is, group A (Topical superoxidised solution dressing) and group B (Topical povidine iodine dressing).

Results

In the present study, 76.67% of patients in group A and B were males and the male to female ratio was 3.2:1. The mean group A was 55.90 ± 14.27 years compared to 51.50 ± 13.18 years in group B. Type 2 diabetes was present in 96.67% and 93.33% of patients in group A and B. The mean initial ulcer area in group A was 3882 ± 1890 mm^2compared to 3992 ± 2000 mm^2in group B. The mean final area in group A was significantly low (1607 ± 862 mm^2) compared to group B (2351 ± 1240 mm^2; p=0.009) and the comparison of mean change in

ulcer area was significantly high in group A compared to group B (2215 ± 1060 mm^2 Vs 1641 ± 856 mm^2; p=0.024). The mean percentage reduction in ulcer area among patients with group A was significantly high (58.90 ± 5.21 percent Vs 40.90 ± 8.76 percent; p=0.024).The commonest organism isolated in group A was Escherichia coli (26.67%) and in group B, it was staphylococcus. The culture was positive in 26% of the patients in group A compared to 50% in group B (p=0.063).

Conclusion and interpretation

Overall, topical superoxidised solution dressings accelerated the healing process resulting in faster recovery through reduction in ulcer area in patients infected with diabetic ulcers compared to topical povidine iodine dressing.

Keywords

Diabetic foot ulcer; Superoxidised solution dressings; Topical povidine iodine;

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Chapter 1

Introduction

INTRODUCTION

Diabetes mellitus (DM) is one of the oldest diseases known to man which was first reported in Egyptian manuscript about 3000 years ago.It can be distinguished into two types namely, type 1 and type 2.It is estimated that 366 million people had DM in 2011; by 2030 this would rise to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors.[1]

Theprevalence of diabetes in India based on the Indian Council of Medical Research (ICMR) multi-centric survey before 30 years was around 2% in urban area and 1% in rural area. In three decades, these rates have raised to 12 to 16% in urban and 3-8% in rural India among adults over 20 years. These represents a 600 to 800% increase in prevalence rates which is unparalleled in any Western nation. Indeed, India is now referred to as the “Diabetic Capital” of the world.[2]

Diabetes is associated with several complications. The complications of diabetes mellitus include retinopathy, nephropathy, and neuropathy (both peripheral and autonomic). The risk for atherosclerotic vascular disease is also increased in persons with DM. The risk for micro vascular and neuropathic complications is related to both duration of diabetes and the severity of

hyperglycemia; the increased risk for vascular disease actually antedates the onset of hyperglycemia to the degree associated with diabetes mellitus.[3]

Every chronic disease brings with it fears, concerns, and people with diabetes face an especially daunting possibility; Infections that never heal, potentially ending in the loss of the limb. Diabetic foot ulcers are estimated to affect 15% of all diabetic individual during their lifetime.Diabetic foot ulcer is a challenging problem to every Surgeon in day to day practice. Patient suffering from diabetic ulcer often requires hospitalization. One of the major causes of non-healing of ulcer in diabetes is infection caused by a variety of micro-organism such as Staphylococcus aureus and Pseudomonas aeruginosa which invade the wound and multiply, producing harmful toxic substances, causing destruction of tissue and disturbance in wound healing.[4] Treatment of these diabetic feet is a major problem. The quest for better control of wound infection is one of the oldest challenges for medical practice.

The effective management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear,[5,6] daily dressings to provide a moist wound environment,[7] debridement, antibiotic therapy (if osteomyelitis or cellulitis is present),[7,8] optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. The role of wound care is crucial in the management of diabetic ulcers. An ideal wound care product in addition to controlling the infection should also protect the normal tissues and not interfere with normal wound healing.[9]

Presently, infected ulcers are being managed by local dressing with agents like Povidine Iodine, EUSOL, Hydrogen Peroxide, Acetic acid, local antibiotics but have their own limitations.

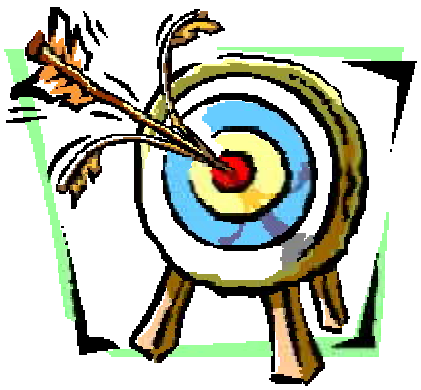
Superoxidised solution is a new concept in wound management with electrochemically processed aqueous solution and neutral pH.Superoxidised solutions may represent an alternative to the currently available antiseptics for the disinfection of wounds.They have shown to be both safe and efficient as a wound care product that moistens, lubricates, debrides and reduces the microbial load of various type of wounds.[10]

They have anti-inflammatory effect and produce an environment with an unbalanced osmolarity that damages the single cell organism. Because the cells of multicellular organisms are tightly bound, preventing the solution from surrounding the cells,there is no shock to the cell membrane and no negative impact. Superoxidised solution is safe as saline and the organisms are least likely to develop resistance as it is due to difference in ionic concentrations. It is significantly less toxic than antiseptic hydrogen peroxide concentrations and it does not induce genotoxicity or accelerated ageing.[11]

However, superoxidised solution, being a new concept,very few studies assessed the role of these dressings in the management of infected diabetic ulcers especially in Indian context. Hence the present study was undertaken to compare the efficacy of dressings with superoxidised solution versuspovidineiodine in the management of infected diabetic ulcers.

Chapter 2

Objective



OBJECTIVE

To compare the efficacy of dressings with superoxidised solution versuspovidine iodine in the management of infected diabetic ulcers.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Approximately 15% of all patients with diabetes will develop a peripheral ulcer. Twenty percent 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 that in a patient without diabetes. The presence of an ulcer in a diabetic patient has a profound 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 nontraumatic 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.[12]

Risk factors

Risk factors for foot ulcers or amputation include male sex, diabetes >10 years duration, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation and poor glycemic control.

Risk Factors for Foot Ulceration and Infection[13]

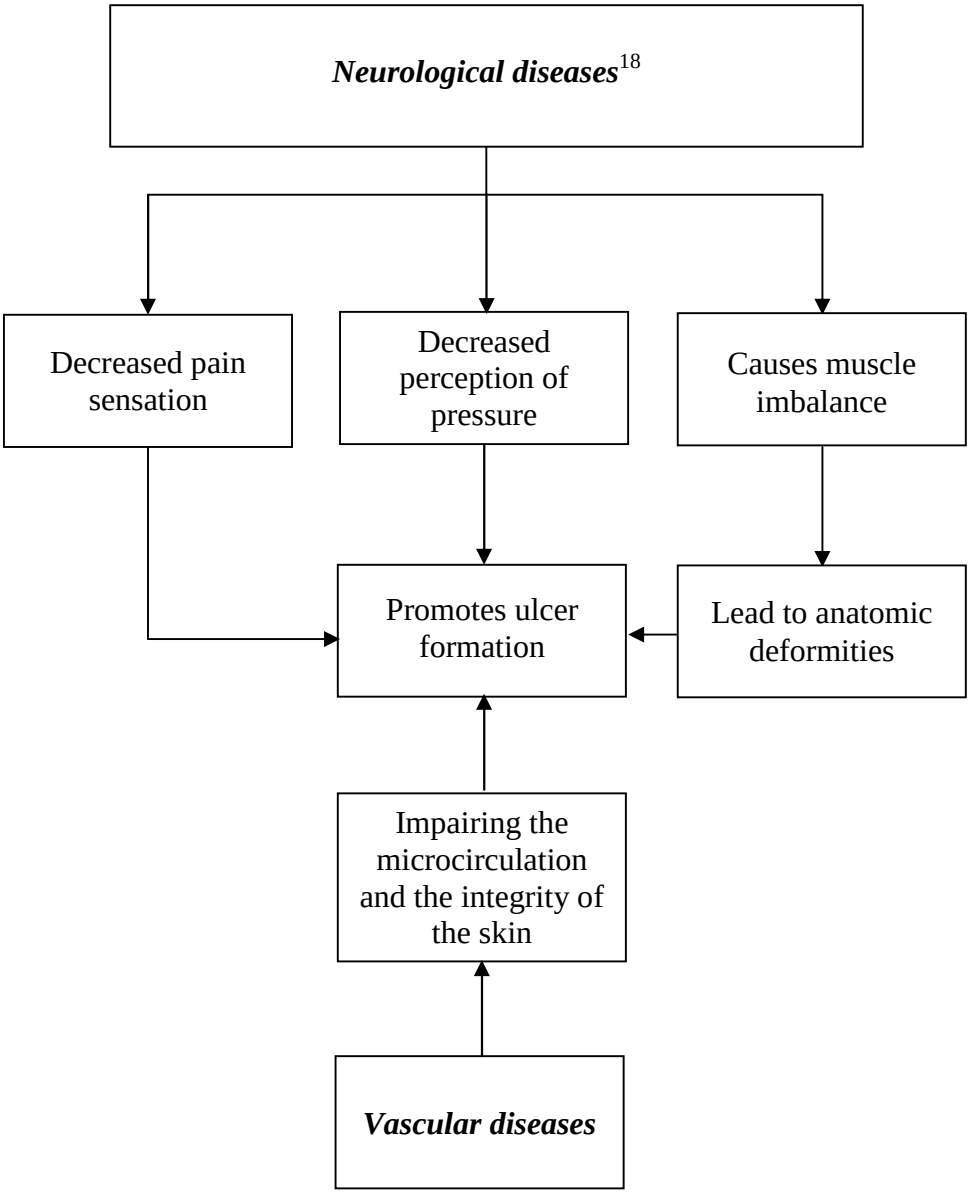
Risk Factor	Mechanism of Injury or Impairment
Peripheral motor neuropathy	Abnormal foot anatomy and biomechanics, with clawing of toes, high arch, and subluxed metatarsophalangeal joints, leading to excess pressure, callus formation and ulcers.
Peripheral sensory neuropathy	Lack of protective sensation, leading to unattended minor injuries caused by excess pressure or mechanical or thermal injury.
Peripheral autonomic neuropathy	Deficient sweating leading to dry, cracking skin.
Neuro-osteoarthropathic deformities (i.e., Charcot disease) or limited joint mobility	Abnormal anatomy and biomechanics, leading to excess pressure, especially in the midplantar area.
Vascular (arterial) insufficiency	Impaired tissue viability, wound healing, and delivery of neutrophils.
Hyperglycemia and other metabolic derangements	Impaired immunological (especially neutrophil) function and wound healing and excess collagen cross-linking.
Patients disabilities	Patient reduced vision, limited mobility, and previous amputation(s).
Maladaptive patient behaviors	Inadequate adherence to precautionary measures and foot inspection and hygiene procedures, poor compliance with medical care, inappropriate activities, excessive weight-bearing, and poor footwear.
Health care system failures	Inadequate patient education and monitoring of glycemic control and foot care.

Etiology

The etiologies of diabetic ulceration include neuropathy,[14] arterial disease,[15] pressure,[16] and foot deformity.[17] Diabetic peripheral neuropathy, present in 60% of diabetic persons and 80% of diabetic persons with foot ulcers, confers the greatest risk of foot ulceration; micro vascular disease and suboptimal glycemic control contribute. Sensory neuropathy involving the feet may lead to unrecognized episodes of trauma due to ill-fitting shoes. Motor neuropathy, causing intrinsic muscle weakness and splaying of the foot on weight bearing, compounds this trauma. The result is a convex foot with a rocker-bottom appearance. Multiple fractures are unnoticed until bone and joint deformities become marked. This is termed a Charcot foot (neuropathic osteoarthropathy) and most commonly is observed in diabetes mellitus, affecting about 2% of diabetic persons. If a Charcot foot is neglected, ulceration may occur at pressure points, particularly the medial aspect of the navicular bone and the inferior aspect of the cuboid bone. Sinus tracts progress from the ulcerations into the deeper planes of the foot and into the bone. Charcot change can also affect the ankle, causing displacement of the ankle mortise and ulceration, which can lead to the need for amputation.

Pathophysiology

Pathogenesis of Diabetic Foot



Neuropathy and diabetes mellitus[19-25]

- The prevalence of diabetic neuropathy in patients with type 2 diabetes is 32 percent overall and more than 50 percent in patients over 60 years of age.
- Diabetic neuropathy correlates with the duration of diabetes and glycemic control) type 1 and 2 DM.
- May manifest as
    1. Polyneuropathy
    2. Mono-neuropathy
    3. Autonomic Neuropathy
- Both myelinated and unmyelinated nerve fibers are affected.
- Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded.

Poly-neuropathy / Mono-neuropathy

- The most common form of diabetic neuropathy is distal symmetric polyneuropathy.
- It presents as:
    1. Distal sensory loss - most frequent presentation
    2. Hyperesthesia
    3. Paresthesia
    4. Dysesthesia

- Symptoms include a sensation of following, which begins in the feet & spreads proximally.
    1. Numbness,
    2. Tingling
    3. Sharpness
    4. Burning

Any combination of these symptoms may develop as neuropathy progresses

- Physical examination reveals
    1. Sensory loss
    2. Loss of ankle reflexes
    3. Abnormal position sense.
- Pain typically involves lower extremities, is usually present at rest, and worsen at night.
- Both an acute (lasting <12 months) and a Chronic form of painful diabetic neuropathy have been described.
- As diabetic neuropathy progresses, the pain subsides & eventually disappears, but a sensory deficit in the lower extremities persists.

Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control.

Autonomic neuropathy

Results in anhydrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation.

The infection and related issues

The source of infection is usually the contamination of the break in the skin, which may be imperceptible like cracks or fissures, puncture wounds or a major wound in a neuropathic foot due to trauma of any cause. Staphylococcus aureus and beta hemolytic streptococci rapidly colonize the break in the skin. A high frequency of anaerobic infection has also been reported.[54] The devastating developments subsequent to an infected ulcer that lead to the development of gangrene, necrotizing fasciitis and life threatening situations like multi organ failure should be guarded against. The pathophysiology of these events can be constructed in the following sequence.

In persons with diabetes, infection results in micro-thrombi formation in the smaller vessels unlike persons without diabetes where it results in vasodilatation. This impairs blood flow in diabetes, converting the small arteries of the toes into end arteries resulting in gangrene of the toes. Osteomyelitis can be difficult to diagnose and remains a focus of uneradicated infection and fails to indicate to the physician the need for longer antibiotic regimen. The diagnosis of Osteomyelitis was missed in as many as two thirds of bone culture proven case. Excessive reliance on plain X rays by primary care physicians does not help. Simple probing the bone can make a diagnosis of Osteomyelitis, while scanning techniques are not always successful, some like Tc99 lack specificity, but MRI is proving helpful.

The risk of lower extremity amputation is 15 to 46 times higher in diabetics than in persons who do not have diabetes mellitus. Foot infections are

the most common complications of diabetic foot and plays a main role in the development of moist gangrene.[26] In general, people with diabetes have infections that are more severe and take longer to cure than equivalent infections in other people. The infection leads to the early development of complication even after a trivial trauma, the disease progresses and becomes refractory to antibacterial therapy.[27] It is essential to assess the magnitude of bacterial infection of the lesions to avoid further complications and save the diabetic foot. Early diagnosis of microbial infections is aimed to institute the appropriate antibacterial therapy and to avoid further complications.[28,29]

However, these infections are difficult to treat because these patients have impaired micro vascular circulation, which limits the access of phagocytic cells to the infected area and results in a poor concentration of antibiotics in the infected tissues. Although infection is rarely implicated in the etiology of diabetic foot ulcers, the ulcers are susceptible to infection once the wound is present.

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.[29] Chronic wounds develop a more complex colonizing flora, including enterococci various Enterobacteriaceae, obligate anaerobes, *Pseudomonas aeruginosa*, and non-fermentative Gram-negative rods.[30] 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]).[31] Although MRSA strains have previously been isolated mainly from hospitalized patients, community associated cases are now becoming common and are associated with poor outcomes in patients with diabetic foot infections.[32]

Pathogens associated with various clinical foot-infection syndromes[13]

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 non-healing wounds with (Y, Z) prolonged broad-spectrum antibiotic therapy	Aerobic gram-positive cocci (Staph aureus, coagulase-negative staphylococci, and enterococci), diphtheroids, Enterobacteriaceae, Pseudomonas species, non-fermentative 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, non-fermentative 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

The impaired host defenses around necrotic soft tissue or bone may allow low-virulence colonizers, such as coagulase-negative staphylococci and *Corynebacterium*species ("diphtheroids"), to assume a pathogenic role. Acute infections in patients who have not recently received antimicrobials are often monomicrobial (almost always with an aerobic Gram-positive coccus), whereas chronic infections are often polymicrobial. The pathogenic role of each isolate in a polymicrobial infection is often unclear.

Recognition of wound infection[33]

The inflammatory response is a protective mechanism that aims to neutralize and destroy any toxic agents at the site of an injury and restore tissue homeostasis. The classic signs of infection include:

- Localized erythema.
- Localized pain.
- Localized heat.
- Edema.

Further criteria include:

- Abscess.
- Discharge which may be viscous in nature, discolored and purulent.
- Delayed healing not previously anticipated.
- Discoloration of tissues both within and at the wound margins.
- Unhealthy granulation tissue.
- Abnormal smell.

- Wound breakdown associated with wound pocketing/bridging at base of wound.

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 Charcot's neuropathy.

Classification

The Wagner system has been widely used for 25 years for grading of diabetic foot ulcer.[34,35]

Wagner Ulcer Classification System

Grade	Lesion
0	No open lesions; may have deformity or cellulitis.
1	Superficial diabetic ulcer (partial or full thickness).
2	Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis.
3	Deep ulcer with abscess, osteomyelitis, or joint sepsis.
4	Gangrene localized to portion of forefoot or heel.
5	Extensive gangrenous involvement of the entire foot.

MEDICAL AND SURGICAL MANAGEMENT[36]

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 at least 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.

Surgical management of Diabetic ulcers

The diabetic ulcers are treated surgically with many modalities.

The treatment depends on grade of the ulcer

Wagner Grade 1 foot

These are patients with superficial ulcers and cellulitis. Infection is controlled with appropriate antibiotics and debridement if required. Ulcers occur because of repetitive pressures Pressure is relieved by complete bed rest, use of total contact cast, walker, braces etc. Associated vascular insufficiency has to be corrected by vascular reconstruction.

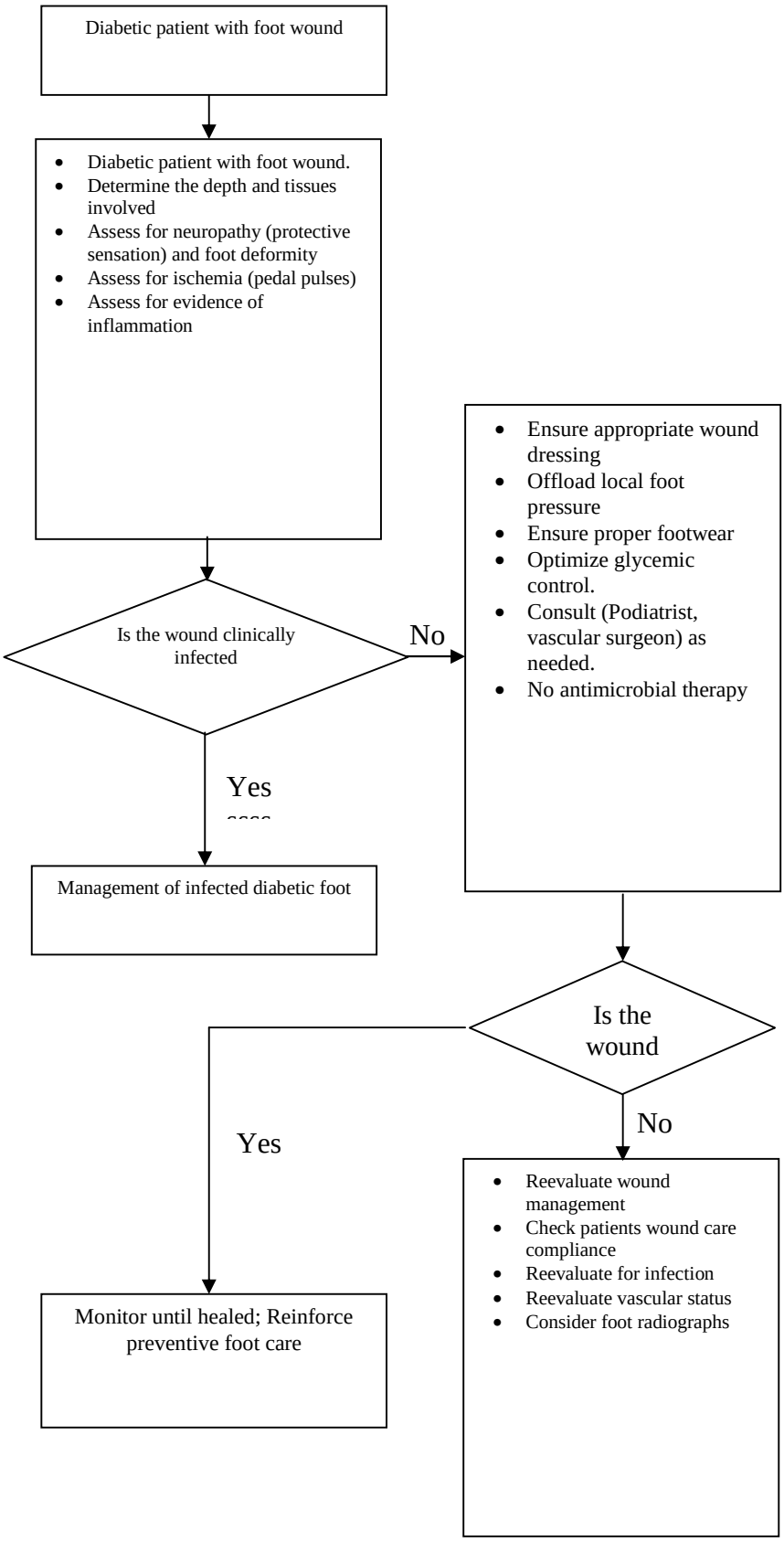
Wagner Grade 2 and Grade 3 feet

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

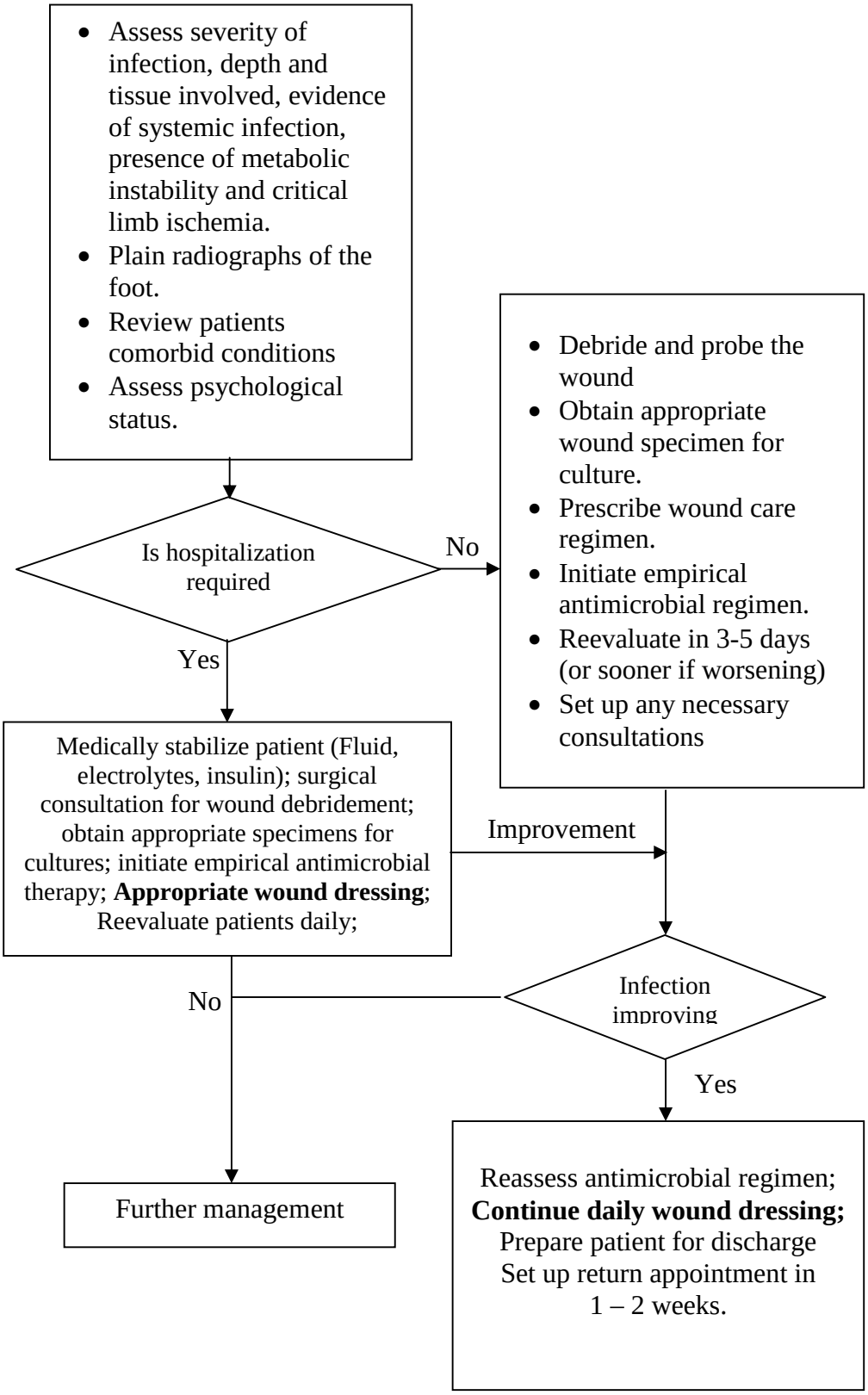
Wagner Grade 4 and 5 feet

These are patients with localized or extensive gangrene. Management is by appropriate minor or major amputation followed by vascular reconstruction.

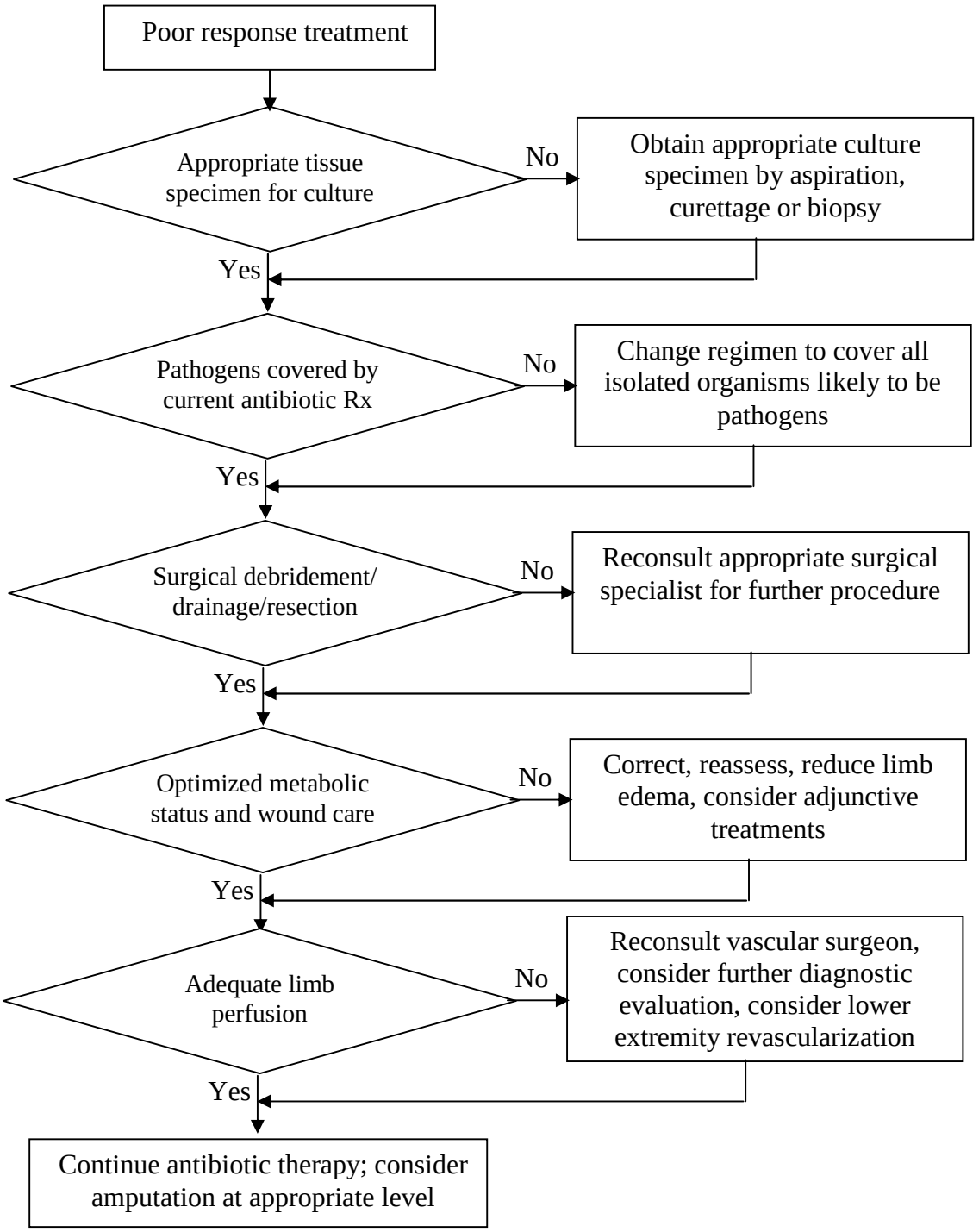
Approach to treating a patient with diabetic foot wound[37]



Approach to the management of infected diabetic foot[37]



Approach to the patient of infected diabetic foot not responding to the treatment[37]



Wound care management

Historical aspects

The earliest documentation concerning wound management is found in the Papyrus Ebers, which dates from around BC 1500 indicating crude treatments based on oiled frog skins, honey, lint and animal grease were commonly used by the Egyptians as wound coverings. An early Hindu document, the SusrutuSanhita reported skin grafts being used as early as BC 700. Jeter and Tintle report that spider's webs, new-born puppies boiled in oil of white lilies, and red-hot pokers to cauterise wounds have been used at various times throughout history. George states that the Sumerians were the first to fashion occlusive dressings, which are capable of maintaining a moist environment, using clay.[38]

In the 19th century, Pasteur advocated that wounds should be covered and kept dry because he believed this would keep them 'germ' free. The dressings developed at this time, made from cloth, cotton and gauze, have dominated wound management in recent history and in some countries they continue to be the main products used. The first manufactured dressings were probably Gamgee wadding and tulle gras. Gamgee discovered that degreased cotton wrapped in bleached lint would absorb fluids, and he introduced his first dressing in the 19th century. During the 1914-18 war, Lumiere in France developed cotton gauze that was impregnated with paraffin to prevent the dressing sticking to the wound. Wound management technology did not progress significantly beyond these early developments until the 1960s, when comparisons were made of wound healing in dry and moist environments. Although initial attempts were made to only alter

the moisture at the surface of a wound, researchers are now investigating the whole wound healing process in order to establish what factors impede wound healing and what characteristics of the environment could be manipulated to accelerate healing.[38]

Moisture and wound healing

In 1962, Winter[39] published his seminal text on the effect of occlusion on wound healing. Winter made experimental wounds in Large-White pigs, and covered half with occlusive film and left the other half exposed to the air. The occluded, and hence moist wounds, had an epithelialization rate twice that of those left to form a scab. Experimental, acute wounds in humans and animals appear to heal more rapidly in a moist environment. The relevance of this to chronic, pathological wounds is unclear.

Role of oxygen in wound healing

Oxygen is essential for cell metabolism, and demand is increased by synthetic processes such as those occurring during wound healing. Shortly after injury, the oxygen tension in a wound falls, so that by day 3, the pO2 in the dead space of a wound is below 10 mmHg. This fall in oxygen tension is accompanied by an increase in the concentration of carbon dioxide, and a fall in pH. A low pO2 provides optimal conditions for fibroblast regeneration, possibly stimulating the process and increasing the rate of advance of granulation tissue.[38]

The concept that hypoxia stimulates healing was further supported by Knighton and co-workers[40] who demonstrated a positive relationship between a steep oxygen gradient between capillaries and hypoxic tissue, and angiogenesis.

pH and wound healing

Few studies have examined the effect of pH on wound healing. In 1973, Leveen[41] demonstrated that the acidification of wound surfaces increased healing. Varghese and co-workers[42] found wound fluid to be more acidic under a Granuflex dressing than under an Opsite dressing, the more acidic pH being compatible with *in vitro* antibacterial activity. However, there are no high-quality randomized controlled trials (RCTs) examining the effects of wound pH on ulcer healing.

Micro-organisms and ulcer healing

The effect of micro-organisms on ulcer healing remains an area of intense debate. That chronic wounds are usually colonized by bacteria is accepted, and an important distinction should be made between colonisation and infection. Infection is characterised by the stigmata of pain, inflammation, purulent exudate and heat, and by the more objective measures of a PMN response and tissue concentrations of organisms in excess of 10^5/g. The effect of occlusive dressings on infection rates is controversial.[38]

Local treatment

Uncontrolled diabetes affects infection and infection adversely affects diabetes.

Dressings

Most foot infections do not require extensive incisions and debridement, yet the principles must always be remembered, Dressings are used to serve the following purposes.[38]

1. Contain wound drainage.
2. Debride a wound
3. Protect an area from trauma
4. Protect an area from contamination
5. Promote proper wound healing

The basic equipment necessary for bedside foot care is

1. Sterile debridement set containing
    a. Sharp scissors for debriding
    b. Blunt ended needle wound probe
    c. Smooth forceps
2. Sterile toenail clippers
3. Sterile gauze dressings
4. Tube gauge, paper tape, culture tubes
5. Medicines
    a. Povidone iodine 2.5% - Bactericidal
    b. Dakin’s solution (chlorazene 0.25%)
    c. Bacitracin ointment — antibacterial
    d. Vaselinegauge
    e. Normal saline

Patients suffering from diabetic foot ulcers need special care. Infection of the diabetic ulcer can have serious consequences. The challenges in treating diabetic foot ulcers includes prolonged hospital stay, high morbidities, medical expenses and sometime leads to lower limb amputation. Dressing is one of the important parts of the treatment of the diabetic ulcer. The types of wound dressing used in diabetic foot ulcer are;[38]

1. Traditional dressing
    a. Gauze dressing with betadine.
2. Modern wound dressing (Occlusive / moist wound dressing)
    a. Alginate Dressings
    b. Amorphous hydrogels
    c. Hydrogel Dressings
    d. Hydrocolloid Dressings
    e. Composite Dressings
    f. Transparent Films

However none of the above mentioned dressings are gold standard in the management of the ulcers.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. Superoxidised solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds. Superoxidised 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.[43]

Povidine Iodine

Povidone-iodine is a multivalent broad spectrum local antiseptic having bactericidal and fungicidal properties. The effect on vegetative cells of various bacteria and fungi is due to the liberation of free iodine from the complex. Many virusses, protozoa, yeasts, cysts and spores are also susceptible.

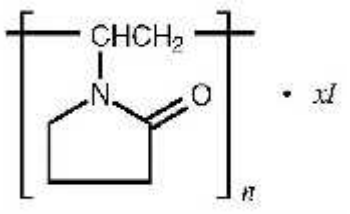


Figure 1. The Chemical structure of Povidine Iodine.

Indications

Disinfection of wounds, lacerations, abrasions and burns. Prophylaxis against infection in hospital and surgery procedures.Preparation of skin and mucous membranes prior to surgery.Post- operative application to protect against infection.Treatment of infected skin conditions.

Contra-indications

- Hypersensitivity to povidone-iodine
- Povidone-iodine solutions should not be used on patients with a non-toxic nodular colloid goiter.Application to large areas of broken skin should be avoided as excessive absorption of iodine may occur.Absorption of povidone-iodine may interfere with thyroid function tests.

Side-effects and special precautions

Local irritation and sensitivity may occur. If irritation, swelling or redness occur, discontinue treatment and consult your physician. Hypothyroidism may occur after topical application to neonates. Absorption of povidone-iodine may interfere with thyroid function tests.

Superoxidised Solutions

Super oxidized solutions on the other hand areelectrochemically processed aqueous solutions manufactured from pure solutions which is rich in reactive oxygen species with neutral pH and longer half life (>12 months). Oxum 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.

Super-oxidized solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds.[44-47] 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.[48] Different super-oxidized solutions have different properties.[49] 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.

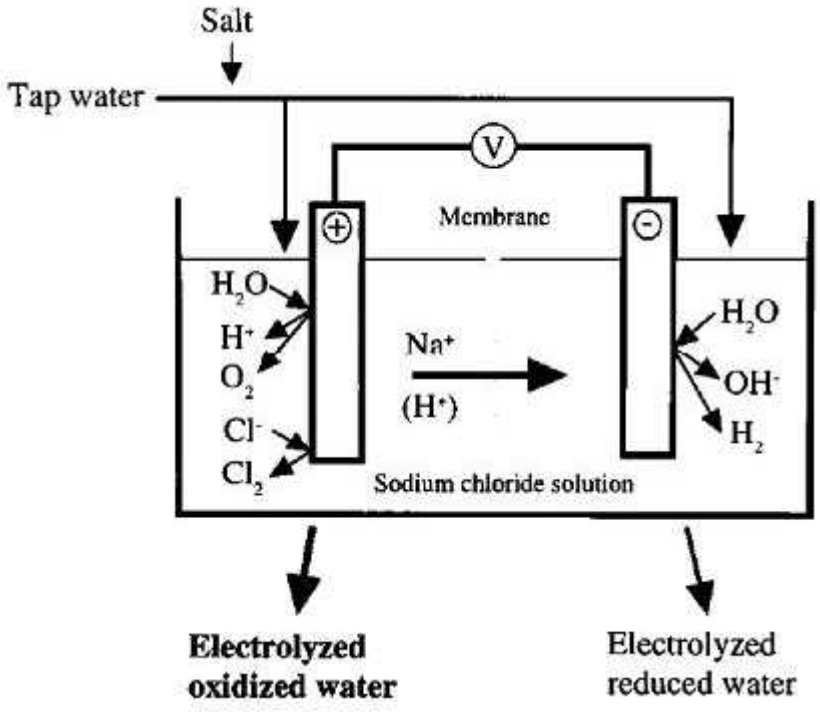


Figure 2. Mechanism of production of Electrolysed water

The ingredients include, oxidized solution (H_2O), sodium hypochlorite (NaOCI), Hypochlorous Acid (HOCI), Hydrogen peroxide (H_2O_2), Ozone (O_3), Chlorine dioxide (ClO_2), Sodium hydroxide (NaOH), Sodium Carbonate (Na_2CO_3) and Sodium chloride (NaCl).

During the electrolysis process, solutions molecules are broken; ions and free radicals are formed. They rapidly react and denature proteins of bacterial cell wall. They also have anti-inflammatory effect and produce an environment with an unbalanced osmolarity that damages single cell organism. The damage is a direct result of the osmolarity difference between the concentrations of the ions in the solution versus the concentration of the same ions in the cell. Multicellular organisms are not prone to such osmolarity changes, therefore host tissues are

spared. Once the single cell membrane is damaged, the ions in the product denature the bacterial proteins as well.[50]

The principle of "Wound Dressing with Super-Oxide Solution"was officially started in the year 2003 when it achieved a status of"Disinfectant and Antiseptic" in its homeland Mexico.[51] Dressingwith super-oxide solution is not a very old topic of discussion andlately a good number of efforts have been made to evaluate theeffectiveness of this approach in wound healing. There have beenisolated reports of its use in healing of diabetic foot ulcers, abscesscavities, surgical wounds and various other types of ulcers.[52]

Theuse of super oxidized aqueous solution for jet lavage debridementhas been found to be as safe and effective as saline.Healing rates have been reported to be significantly shorter incases dressed with super oxide solution. Also duration for culturesto become negative and of antibiotic therapy were also reported tobe shorter. Super oxide solution has been found to be safe andeffective in the management of wide postsurgical lesions in theinfected diabetic foot. Further, this solution hasbeen used in management of chest wall infections and reportedlyreduced the time of healing in a significant manner.[53]

Several studies have shown the efficacy of the superoxidised solutions and its wide range of applications on several types of wounds.A study done by Kapur V et al[10] in Amritsar during 2008 to evaluate the effect and comparison of Superoxidised solution and Povidine Iodine in different types of wounds. Superoxidised solution was safe and effectivein all types of wounds .No systemic and local allergic manifestations noted.Another study by Abhyankar S et al[54]

during 2009 in Mumbai on Efficacy and safety of Superoxidised solution in treatment of chronic wounds has been concluded that the super oxidized solution is novel technology innovation in therapy of chronic wounds. But however both oxum and povidine iodine treated groups showed similar results with regards to decrease in edema, erythema and granulation.

A study conducted by Hadi SF et al[55]in Islamabad in 2006 on treating infected diabetic wounds with Super oxidized water as antiseptic agent : A preliminary Experience revealed that although the initial results of employing Superoxidised water for the management of infected diabetic wounds are encouraging, further multicenter clinical trials are warranted before this antiseptic is recommended for general use. It may offer an economical alternative to other expensive antiseptics with positive impact on the prevailing infection rates, patient outcomes and patient satisfaction.

A study conducted by Gonzalez D et al[56]on effects of pH neutral superoxided solutions on human dermal fibroblasts in vitro stated that Superoxidised solution is significantly less cytotoxic than the Hydrogen peroxide concentrations and it does not induce genotoxicity or accelerated ageing in vitro.

A study done by Espinosa G et al[57] in Mexico on effects of pH-neutral, Superoxided solution on human dermal fibroblasts in vitro concluded that Superoxidised solution is significantly less toxic than hydrogen peroxide and that it does not induce genotoxicity or accelerated ageing.However a major concern when using the Superoxidised solutions is the potential induction of oxidative stress in human dermal fibroblasts). A study conducted by Dharap S et al[58] on

efficacy and safety of oxum in treatment of the venous ulcers demonstrated that Superoxidised solution improved the clinical status,reduced the signs of inflammation in venous ulcers in addition to its well confirmed anti-infective properties.

Areport by Bryant cited an unpublished study where superoxidesolution was used, found that it reduced the average hospital stayfor patients with second and third degree burns from 28 days to 14days, and reduced the need of antibiotics.[53]

In a conference presentation Allie et al[59] describedcomparison in patients with lower extremity ulcer treated withsuper-oxide solution with matched historical group who receivedtraditional wound care. They found no local complications and theulcers healed in 98% patients of SOS group compared with 92% oftraditional wound care group. In 300 neuropathic diabetic patientsonly a very few experienced pain with super- oxide solution.Reports indicate that super oxidised solution has helped incomplete healing of wounds, and prepared wounds for definitecover in diabetic foot patients with minimal side effects.[60]

Wolvos TA[61] used Superoxidised solution to treat 26 patients with various wound types that included 9 patients with post-operative wound. He concluded that Superoxidised 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.

A Study conducted by Dr. Luca Dalla Paola[62] on 218 patients suffering from chronic diabetic foot ulcers 110 patients were treated with SOS(oxum) and 108 patients with povidine iodine. The mean healing time was lower in the oxum group (45±14) days v/s (58±20) days in betadine group.Gutierrez in his study to explore various applications of superoxidised solutions concluded that the moistening effects and minimum toxicity found with the use of this superoxidised solution made it a good choice for wound care management.[63]

Prevention of diabetic foot ulcers

Prevention of ulceration and recurrence once ulceration has occurred are the ultimate goals of any modern team approach to the diabetic foot. Wagner's Grade 0: Foot are the patients who are potentially "at risk" to develop ulcer or infection due to varying degree of neuropathy and joint deformities, They need regular assessment annually for neuropathy and vascular status. Hence the role of proper footwear and hygiene cannot be overemphasized. The diabetic patient and his family must establish a routine for daily foot and shoe inspection and hygiene. Every patient must be taught to shake his shoes at and inspect them prior to wearing. Proper hygiene must become a religion. Washing the feet everyday with mild soap and rinsing and drying thoroughly especially between the toes are advised. The physician or health care provider must always set the example. Controlling blood glucose, weight, and blood pressure; eliminating smoking; encouraging daily exercises are important, Periodical neurological and vascular examinations are important. Early recognition and prompt reporting of a problem are encouraged.

Chapter 4

Methodology

METHODOLOGY

Study design

The study design was randomized controlled trial.

Study period and duration

The present study was conducted for the period of one year from January 2012 to December 2012.

Place

This study was carried out in the Department of General Surgery, KLES Dr.PrabhakarKoreHospital and Medical Research Centre, Belgaum attached to KLEUniversity'sJawaharlalNehruMedicalCollege, Belgaum.

Source of Data

Patients presenting with infected diabetic ulcers to the Department of General Surgery, KLES Dr. PrabhakarKoreHospital and Medical Research Centre, Belgaum were studied.

Sample size

A total of 60 patients divided into two groups of 30 each.

Sampling procedure

Due to the scarcity of literature on efficacy of dressings with superoxidised solution by applyingthumb rule, a total of 60 cases were taken up for the study.

Selection criteria

Inclusion

- Diabetic patients of age more than 20 years.
- Patients with controlled diabetes with fasting blood glucose levels less than 126 mg/dL.
- Patients having infected diabetic ulcers measuring more than 1cms, with slough, foul smell and minimal granulation tissue.
- Patients with grade1 and grade 2 of Wagner's classification.

Exclusion

- Grade 3, 4, 5 Wagner's classification.
- Absent peripheral pulses.
- Patients who are not regular on follow up.
- Patients not willing to enroll in the study.

Ethical clearance

Prior to the commencement, thestudy was approved from the Ethical and Research Committee, JawaharlalNehruMedicalCollege, Belgaum.

Informed Consent

Patientsfulfilling selection criteria were informed about the nature of the study, and a written informed consent was obtained (Annexure I).

Randomization

Patients were divided into two groups of 30 each by computer generated random numbers as below;

- Group A – Patients in this group received dressing with topical superoxidised solution.
- Group B – Patients in this group received dressing with topical povidine Iodine solution.

Method of collection of data

Demographicdata such as age,sex and ulcer details were obtained through an interview. Details such as duration and type of diabetes, diabetic treatment,ulcer site, discharge were noted. Further these patients were subjected to clinical examination and the findings were noted on a predesigned and pretested proforma (Annexure II).

Investigations

The patients were subjected to the following investigations.

- Complete blood count.
- Fasting blood sugar

- Protein levels
- Blood Urea and Serum Creatinine
- Culture and antibiotic sensitivity.
- Colour Doppler (whenever required).
- X-Ray foot –AP and Lateral view (whenever required).

Procedure

Wound discharge was sent for culture and sensitivity. Empirical antibiotics – Ciprofloxacin and Metronidazole were started and changed to sensitive antibiotics after sensitivity report. The culture was repeated after 10 days of the dressing and Debridement was done if necessary.

Dressing

- In group A, topical superoxidised solution was sprayed and gauze soaked in the superoxidised solution placed on the wound and dressing done.
- In Group B, wound was cleaned with povidine iodine and gauze soaked in povidine iodine placed on the wound and dressing done.

Outcome variables

Ulcer size

Ulcer size was assessed at the end of every 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 was considered as the size of the wound. It was

done for two weeks. Wound was observed for granulation, tissue quality and discharge from the wound at the end of each week.

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 Fishers exact test. Continuous data was expressed as mean ± standard deviation and the comparison was done using unpaired 't' test. A 'p' value of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

RESULTS

This randomized controlled trial was carried out in the Department of General Surgery, KLES Dr.PrabhakarKoreHospital and Medical Research Centre, Belgaum attached to KLE University's JawaharlalNehruMedicalCollege, Belgaum.

A total of 60 patientspresenting with infected diabetic ulcersdivided into two groups of 30 each. Patients were divided into two groups of 30 each by computer generated random numbers as below;

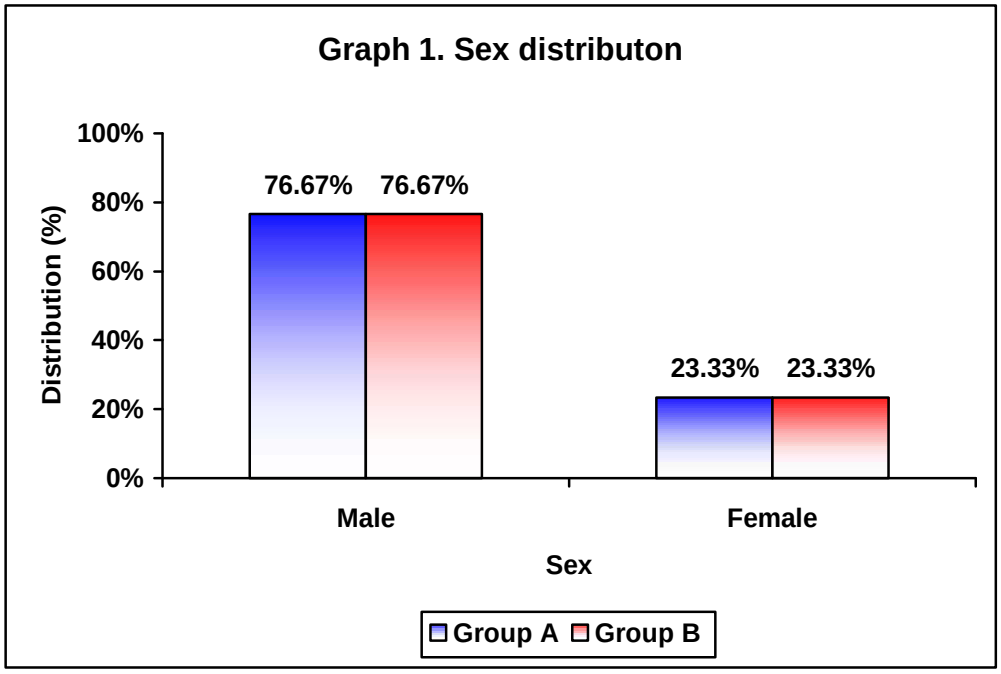
- Group A – Patients in this group received dressing with topical superoxidised solution.
- Group B – Patients in this group received dressing with topical povidine Iodine solution.

The data obtained was coded and entered into the Excel spreadsheet (Annexure IV). The data was analyzed and the final observations and results were tabulated as below

Table 1. Sex distribution

Sex	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Male	23	76.67	23	76.67
Female	7	23.33	7	23.33
Total	**30**	**100.00**	**30**	**100.00**

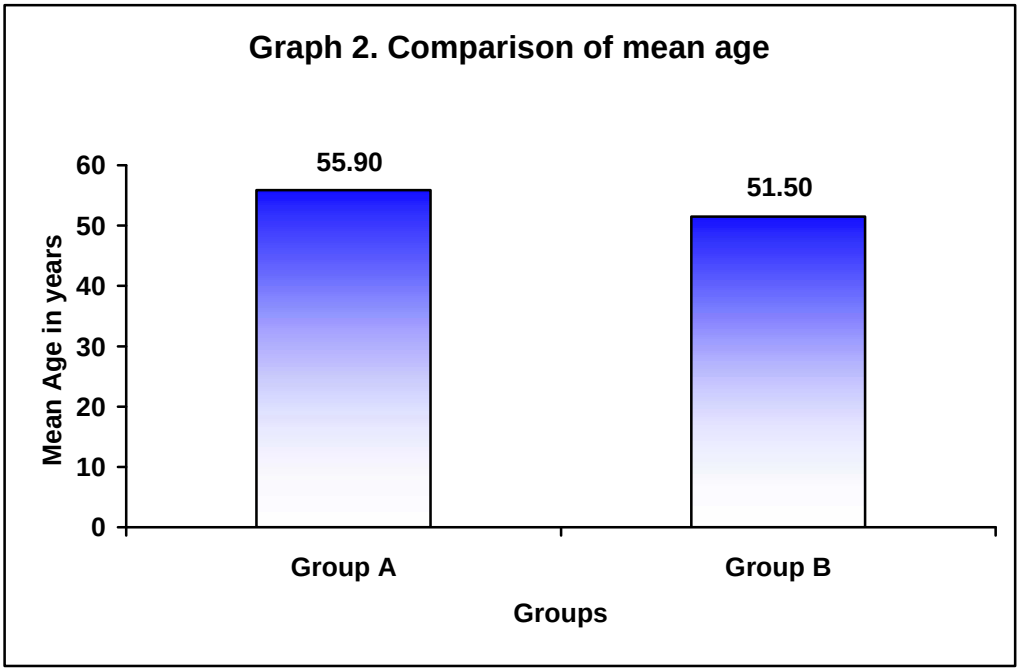
p = 1.000



In the present study, 76.67% of patients in group A and B were males compared to 23.33% of females and the male to female ratio was 3.2:1. The sex distribution in group A and B was comparable (p=1.000)

Table 2. Comparison of mean age

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Age (Years)	55.90	14.27	51.50	13.18	0.227

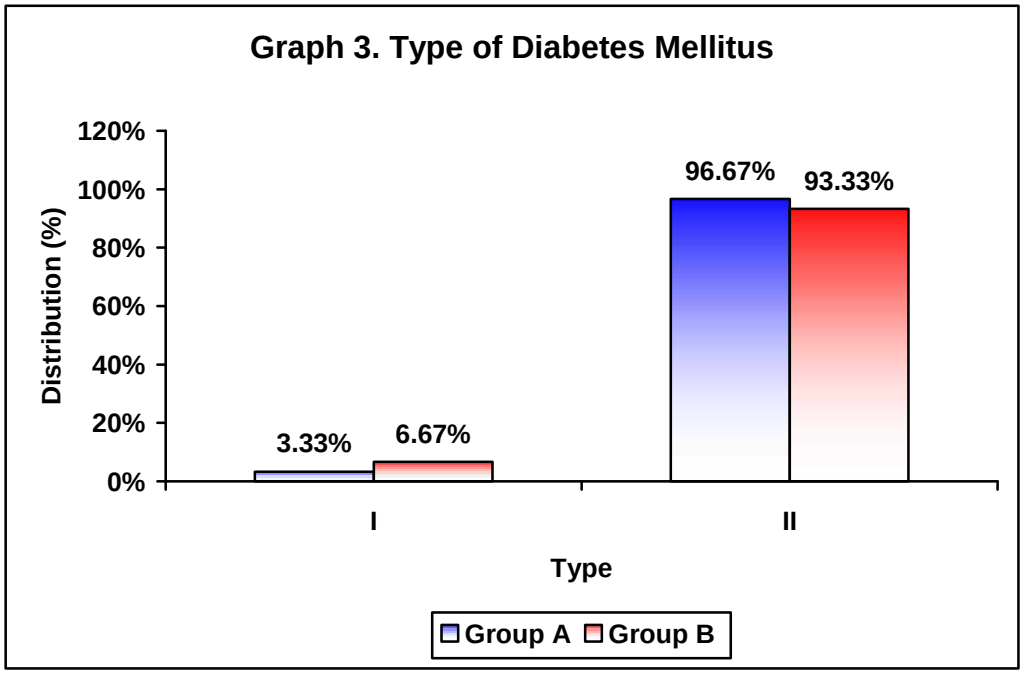


In this study the mean age of group A was 55.90 ± 14.27 years compared to 51.50 ± 13.18 years in group B (p=0.227).

Table 3. Type of Diabetes Mellitus

Type	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
I	1	3.33	2	6.67
II	29	96.67	28	93.33
Total	**30**	**100.00**	**30**	**100.00**

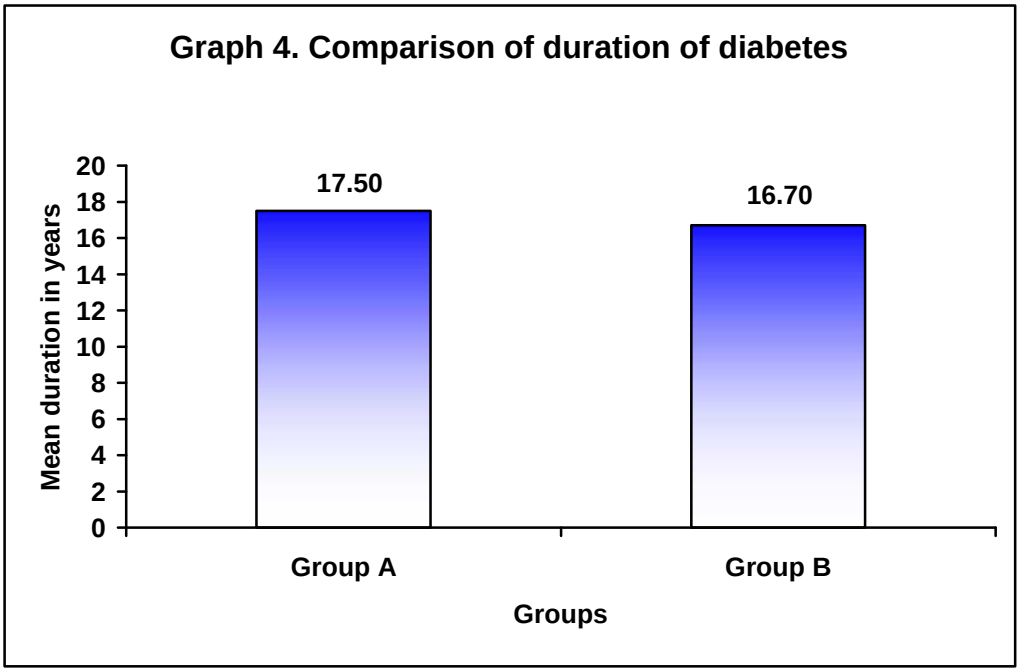
p = 0.554



In the present study 96.67% of patients in group A had type 2 diabetes mellitus and in group B, the same type was noted in 93.33% (p=0.554).

Table 4. Comparison of duration of diabetes

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Duration (Years)	17.50	9.46	16.70	7.12	0.550

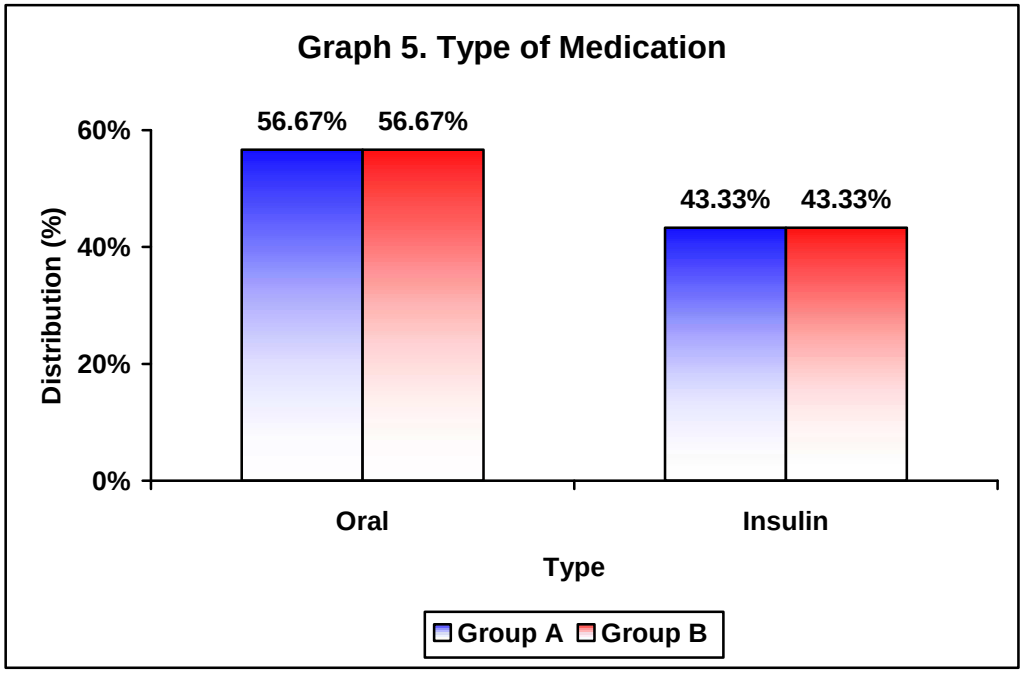


In this study the mean duration of diabetes in group A and B was comparable (17.50 ± 9.46 vs 16.70 ± 7.12; p=0.550).

Table 5. Type of Medication

Type	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Oral	17	56.67	17	56.67
Insulin	13	43.33	13	43.33
Total	**30**	**100.00**	**30**	**100.00**

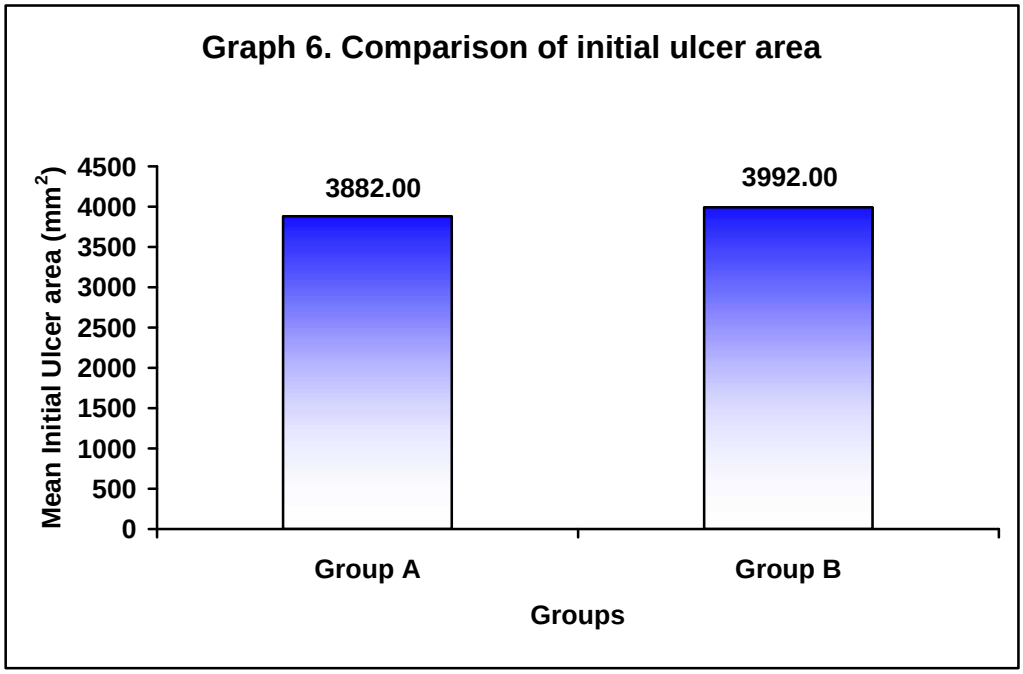
p = 1.000



In the present study, 56.67% of patients in both the groups were on oral medication and 43.33% were on insulin. The treatment received in patients of group A and B was comparable (p=1.000).

Table 6. Comparison of initial ulcer area

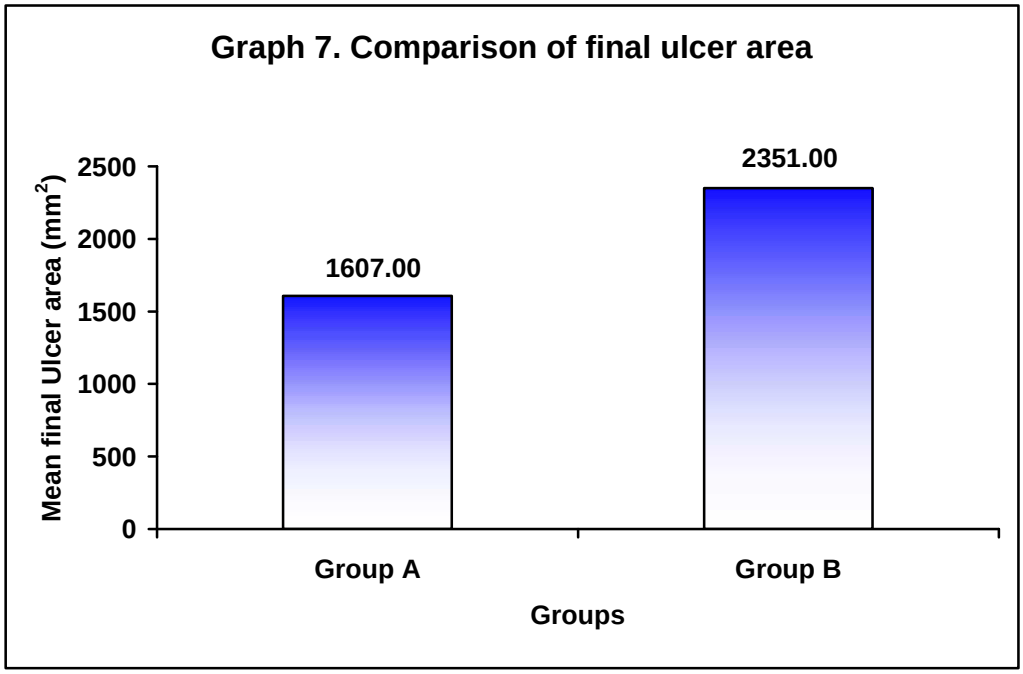
Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Ulcer area (mm^2)	3882.00	1890.00	3992.00	2000.00	0.736



In this study, the mean initial ulcer area in group A was low (3882 ± 1890 mm^2)compared to group B (3992 ± 2000 mm^2). However , the difference was statistically not significant (p=0.736).

Table 7. Comparison of final ulcer area

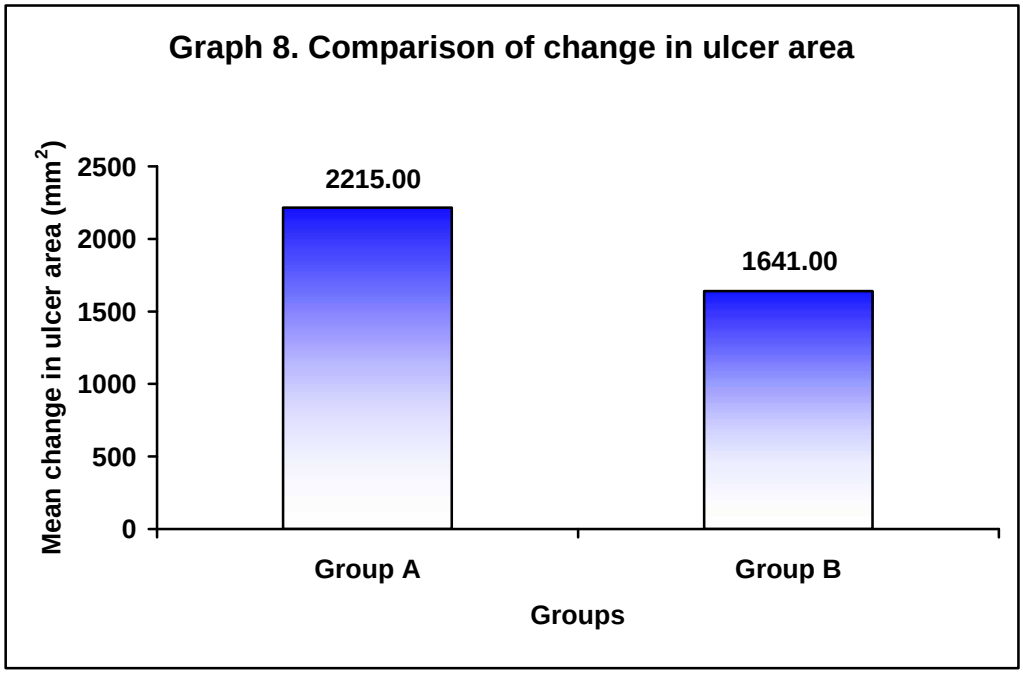
Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Ulcer area (mm^2)	1607.00	862.00	2351.00	1240.00	0.009



In the present study the mean final area in group A was significantly low (1607 ± 862 mm^2)compared to group B (2351 ± 1240 mm^2; p=0.009).

Table 8. Comparison of change in ulcer area

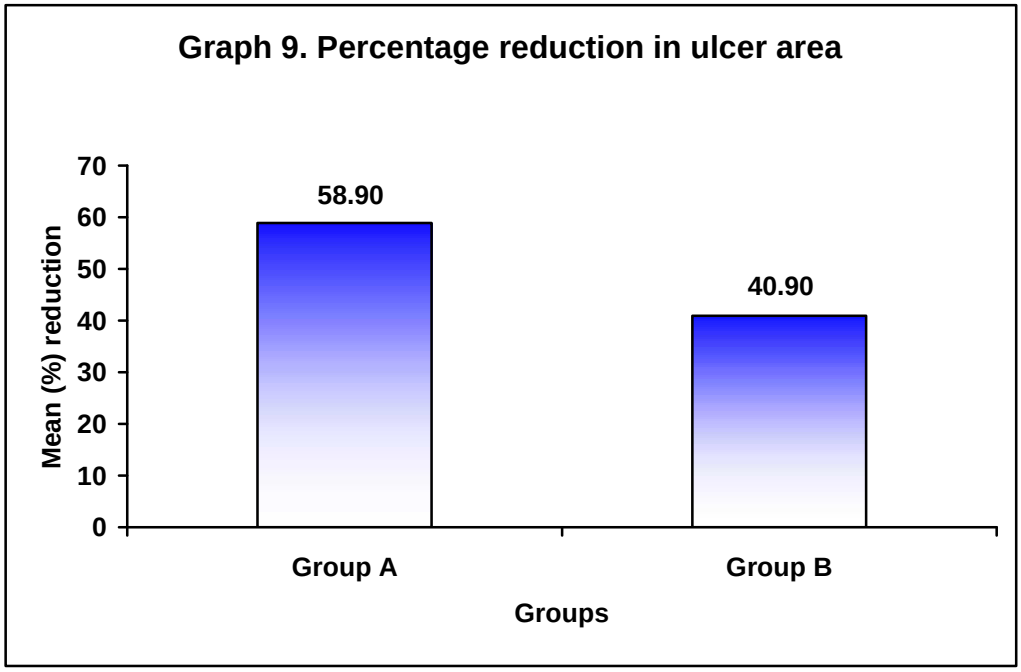
Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Ulcer area (mm^2)	2215.00	1060.00	1641.00	856.00	0.024



In this study the comparison of mean change in ulcer area in group A was significantly high (2215 ± 1060 mm^2)compared to group B (1641 ± 856 mm^2; p=0.024).

Table 9. Percentage reduction in ulcer area

Variables	Group A (n=30)		Group B (n=30)		p value
	Mean	SD	Mean	SD	
Percentage reduction	58.90	5.21	40.90	8.76	<0.001



In the present study the mean percentage reduction in ulcer area among patients with group A was 58.90 ± 5.21 percent compared to 40.90 ± 8.76 percent. This difference was statistically significant (p=0.024).

Table 10. Organisms isolated in initial culture

Organism	Group A (n=30)		Group B (n=30)	
	No.	**%**	**No.**	**%**
E. coli	8	26.67	6	20.00
Staphylococcus	1	3.33	9	30.00
Proteus	3	10.00	5	16.67
Pseudomonas	8	26.67	5	16.67
Klebsiella	2	6.67	0	0.00
Streptococcus	3	10.00	2	6.67
Klebsiella + E. coli	0	0.00	2	6.67
Staphylococcus + pseudomonas	0	0.00	1	3.33
Acinobacter	3	10.00	0	0.00
Acinobacter + E. coli	1	3.33	0	0.00
E. coli = proteus	1	3.33	0	0.00
Total	**30**	**100.00**	**30**	**100.00**

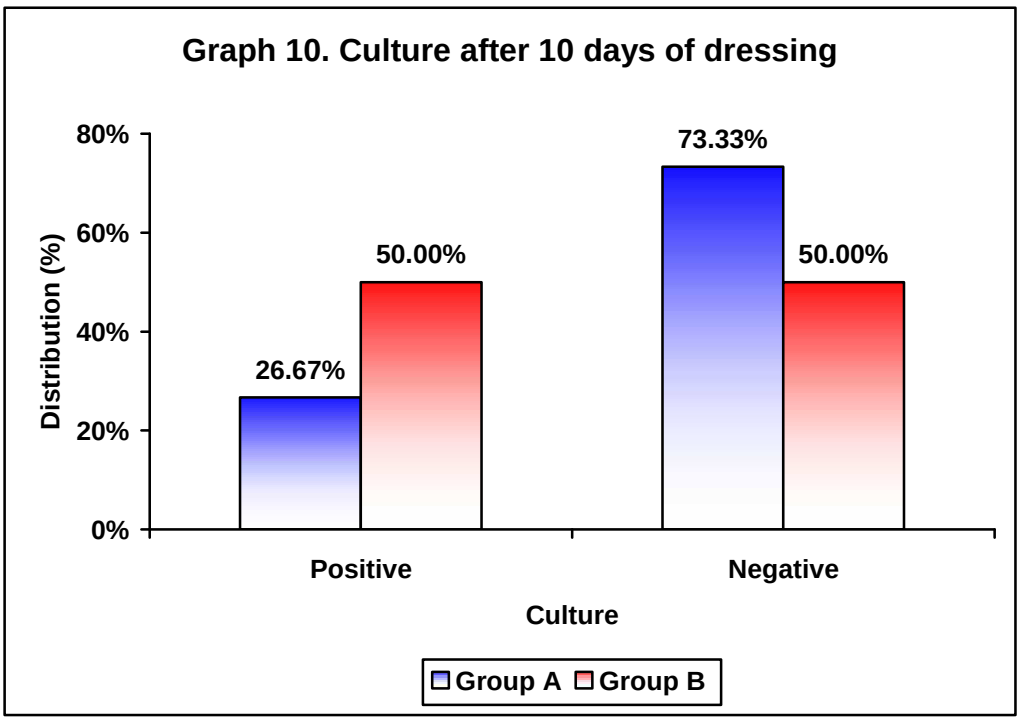
p = 0.025

Table 10 shows organisms isolated from the culture. The commonest organism isolated in group A was E.coli (26.67%) and in group B staphylococcus was the commonest organism. The distribution of other organisms is as shown in Table 10.

Table 11. Culture after 10 days of dressing

Culture	Group A (n=30)		Group B (n=30)	
	Number	**Percentage**	**Number**	**Percentage**
Positive	8	26.67	15	50.00
Negative	22	73.33	15	50.00
Total	**30**	**100.00**	**30**	**100.00**

p = 0.063



In this study higher number of patients had positive culture in group B (50%) compared to group A (26.67%) after 10th day of dressing. However this difference was statistically not significant (p=0.063).

Chapter 6

Discussion

DISCUSSION

The incidence of DM is increasing in the present scenario because of sedentary life style, change in dietary habits, increase in stress, and increase in life span of human being. Management of DM and its complications is a complex procedure involves all specialties as it involves all organs and systems of the body. If glycemic control is not adequate, patients present with various complications like diabetic ulcers which are caused by trivial or noticeable trauma.

Foot ulceration is the precursor to approximately 85% of all diabetic amputations, and it is estimated that 14%–20% of patients with foot ulcers will have to undergo amputation. Infection of the ulcer increases the risk of amputation. If patients with ulcers are initially treated by a multidisciplinary team, major amputations can be prevented in 80%–90% of cases of limb-threatening ischemia and in 95% of patients with infection. This is significant, because amputations are related to high morbidity and mortality.[62]

Diabetic foot ulcer is a challenging problem to every clinician in day to day practice. The most widely used therapies for treating foot ulcers are operative procedures and systemic antibiotics, highlighting the importance of infection control. Topical antiseptics are used to reduce the microbial load in both intact skin and in wounds. Antiseptics have been used in preference to topical antibiotics because of concerns about the development of bacterial resistance. However, the cytotoxic effects of these agents on the host's dermal and epidermal cells may affect the wound healing process.[62] These wounds have been managed

by local dressings with various agents like Povidine Iodine, EUSOL, Acetic acid, hydrogen peroxide, Silver sulfadiazine, local antibiotic ointments or powders etc. since long time.[64]

The treatment of Super Oxidized Solution in the wound management remains less understood being newer concept. The present study was aimed to compare the efficacy of dressings with superoxidised solution versus povidine iodine in the management of infected diabetic ulcers.

This one year randomized controlled trial was done on a total of 60 patients presenting with infected diabetic ulcers from January 2012 to December 2012 in the Department of General Surgery at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. The patients were divided into two groups of 30 each based on computer generated randomization viz., group A where patients received topical superoxidised solution dressing and group B where patient received topical povidine iodine dressing.

In this study, 76.67% of patients were males in group A and B compared to 23.33% of females. The male to female ratio was 3.2:1. Though there was male preponderance the sex distribution between group A and B was comparable (p=1.000). The mean age of group A was slightly high (55.90 ± 14.27 years) compared to group B (51.50 ± 13.18 years) but the difference was statistically not significant (p=0.227).

In the present study maximum patients presented with type 2 DM. In group A, 96.67% of the patients were noted with type 2 DM compared to 93.33% of the patients in group B. Though higher proportionate patients with type 2 DM

were observed in both the groups, the comparison between group A and B showed equal distribution (p=0.554). Among the patients in group A, the mean duration of diabetes was slightly high compared to group B but, the difference was statistically not significant (17.50 ± 9.46 vs. 16.70 ± 7.12; p=0.550). The treatment of DM was oral medications in 56.67% of patients in both the groups compared to 43.33% of patients who were on insulin. However, the treatment received in patients of group A and B was comparable (p=1.000).

In this study, the mean initial ulcer area in group A was 3882 ± 1890 mm^2 compared to group B which was 3992 ± 2000 mm^2 ,however the difference was statistically not significant (p=0.736). The above findings on age, sex, diabetic history including type, duration, and treatment and the ulcer characteristics were comparable in both the groups.

In this study the final mean ulcer area in group A was found to be significantly low compared to group B (1607 ± 862 versus 2351 ± 1240 mm^2; p=0.009). The comparison of mean change in ulcer area was also significantly high in group A that is, 2215 ± 1060 mm^2 compared to group B that is, 1641 ± 856 mm^2 (p=0.024). Similarly the mean percentage reduction in ulcer area in group A was significantly high that is, 58.90±5.21 percent compared to 40.90±8.76 percent in group B (p=0.024). In this study, Escherichia coli and pseudomonas were the commonest organisms isolated in patients with group A (26.67% each) followed by Streptococcus, Proteus and Acinobacter (10% each), Klebsiella (6.67%), Staphylococcus, Acinobacter with Escherichia coli and Escherichia coli with Proteus (3.33% each). In group B, staphylococcus (30%) was the commonest organism isolated while and Escherichia coli, Pseudomonas,

Streptococcus and Proteus were seen in 20%, 16.67%, 6.67% and 16.67% of the patients respectively. The other organisms in group B included Staphylococcus with pseudomonas and Klebsiella with Escherichia coli (3.33% each.

In the study, higher number of patients in group B had positive culture (50%) compared to group A (26.67%) but this difference was statistically not significant (p=0.063). Similar findings were reported in a study by Kapur V et al[10] where the swab culture was positive in 105 out of a total of 200 patients.

These findings suggest that, the patients in group A, who received topical superoxidised solution dressing had significantly favorable outcome in terms of reduction in ulcer area there by faster recovery from wound compared to group B where patient received topical povidine iodine dressing. Superoxidised solutions have been proved safe and effective in post-surgical wound management. However, studies comparing the safety and efficacy of topical superoxidised solution dressing in diabetic foot ulcers are scarce.

An open-label study evaluated the efficacy of a novel superoxidised solution compared with a standard treatment (10% povidine iodine solution [PI]) in treating diabetic foot lesions grades 2 and 3 that were infected. Patients in the superoxidised solution group had significantly shorter median healing time compared with patients in the povidine iodine group (43 days versus 55 days, $P < 0.0001$). No skin reactions occurred in the superoxidised group in contrast to 18 patients in the povidine iodine group who did experience skin reactions. The authors concluded that, superoxidised solution is effective and safe in treating

infected foot lesions when included within a comprehensive wound care regimen.[62]

Another study by Kapur V, et al[10] in India demonstrated that, diabetic foot ulcer and chronic leg ulcers patients treated with superoxidised solution shows early granulation and rapid epithelisation when compared to betadine group. In their study the mean follow up of 21 days showed average reduction in wound size and periwound edema/erythema in oxum group as 70% as compared to 50% in betadine group. Also, authors reported that, average reduction in wound size and periwound oedema/erythema was more with superoxidised solution. Pus discharge reduced earlier with early appearance of granulation and epithelisation proving oxum to be safe and efficient as a wound care product superior to povidine iodine. In a study by Kapur V et al,[10] most commonly cultured organisms was Staph aureus 42 (40%) followed by E. coli 37(35.2%), pseudomonas 15(14.3%), Streptococcus 11(10.5%). The findings of the present study were comparable with the study done by Kapur V et al.[10]

A study was done by Abhyankar S et al[54] during 2009 in Mumbai on Efficacy and safety of Superoxidised solution in treatment of chronic wounds. It has been concluded that the Superoxidised solution is novel technology innovation in therapy of chronic wounds. But however both oxum and povidine iodine treated groups showed similar results with regards to decrease in edema, erythema and granulation. Unlike our study there was no clear advantage of SOS over PI.

A study done by Espinosa G et al[56] in Mexico on effects of pH-neutral, Superoxidised solution on human dermal fibroblasts in vitro concluded that Superoxidised solution is significantly less toxic than hydrogen peroxide and that it does not induce genotoxicity or accelerated ageing. However in our study there were no side effects / intolerance noted.

A study conducted by Dharap S et al[58] on efficacy and safety of superoxidised solution in treatment of the venous ulcers demonstrated that Superoxidised solution improved the clinical status, reduced the signs of inflammation in venous ulcers in addition to its well confirmed anti-infective properties

Wolvos TA[61] used superoxidised solution to treat 26 patients with various wound types that included 9 patients with post-operative wound. In these patients, the wounds including those with complications healed completely with dressings of wound with superoxidised solution. He concluded that Superoxidised 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.

Gutierrez AA[63] in his study to explore various applications of Superoxidised solution concluded that the moistening effect and the minimum toxicity found with the use of this superoxidised solution makes it a good choice for wound care management and that this non-antibiotic technology appears to

offer a broad new paradigm for the prevention and treatment of acute and chronic wounds.

The SOS could be an alternative to these agents, as it has shown antimicrobial efficacy without inducing toxicity, even against antibiotic-resistant bacteria, such as MRSA. Reactive chlorine and oxygen species in SOS denature bacterial cell wall, which has been previously reported. However, SOS has not been shown to induce cytotoxicity in fibroblast cultures in vitro and does not interfere with the wound healing process, which has been shown by histopathological and immunohistochemical analyses of wounds that had been treated with this solution.[62]

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. Superoxidised solutions may represent an alternative to the currently available antiseptics for the disinfection of skin and wounds. Superoxidised 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.[43]

The limitation of the study was that, the study included all the diabetic cases (type 1 and 2) so the specific outcomes in different types of diabetes could not be drawn. Further studies with large sample, considering specific diabetic types and glycemic control may enlighten the precise role of superoxidised solution in the management of diabetic foot ulcers.

Chapter 7

Conclusion

CONCLUSION

Based on the results of this study it may be concluded that, topical superoxidised solution dressings had beneficial effect in terms of reduction in ulcer area and thereby accelerating faster recovery in the management of infected diabetic ulcers compared to topical povidine iodine dressing.

Chapter 8

Summary

SUMMARY

Diabetic foot ulcer is a challenging problem to every clinician in day to day practice. Superoxidised Solution is a newer concept in the wound management. The present study was aimed to compare the efficacy of dressings with superoxidised solution versus povidine iodine in the management of infected diabetic ulcers.

This one year randomized controlled trial was conducted on a total of 60 patients presenting with infected diabetic ulcers from January 2012 to December 2012 in the Department of General Surgery at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. The patients were divided into two groups of 30 each based on computer generated randomization that is, group A (Topical superoxidised solution dressing) and group B (Topical povidine iodine dressing).

In the present study, 76.67% of patients in group A and B were males and the male to female ratio was 3.2:1. The mean group A was 55.90 ± 14.27 years compared to 51.50 ± 13.18 years in group B. Type 2 diabetes was present in 96.67% and 93.33% of patients in group A and B. The mean duration of DM in group A was 17.50 ± 9.46 and in group B, it was 16.70 ± 7.12 years. Treatment with oral medications was noted in 56.67% of patients in both the groups. The mean initial ulcer area in group A was 3882 ± 1890 mm^2 compared to 3992 ± 2000 mm^2 in group B. The mean final area in group A was significantly low (1607 ± 862 mm^2) compared to group B (2351 ± 1240 mm^2; p=0.009) and the comparison of mean change in ulcer area was significantly high in group A

compared to group B (2215 ± 1060 mm^2 Vs 1641 ± 856 mm^2; p=0.024). The mean percentage reduction in ulcer area among patients with group A was significantly high (58.90 ± 5.21 percent Vs 40.90 ± 8.76 percent; p=0.024). The commonest organism isolated in group A was Escherichia coli (26.67%) and in group B, it was staphylococcus. The culture was positive in 26% of the patients in group A compared 50% in group B after 10 days of dressings with respective agents (p=0.063).

Overall, topical superoxidised solution dressings accelerated the healing process resulting in faster recovery through reduction in ulcer area in patients with infected diabetic ulcers compared to topical povidine iodine dressing.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

A RANDOMISED CONTOL TRIAL TO COMPARE EFFICACY OF DRESSINGS WITH SUPEROXIDISED SOLUTION VERSUS POVIDINE IODINE IN MANAGEMENT OF INFECTED DIABETIC ULCERS.

Principal Investigator:
Dr. ******** ** **
Professor,
Department Of General Surgery,
J. N. Medical College, Belgaum.

Co-investigator:
Dr. ******* ********
Post Graduate Student,
Department Of General Surgery,
J. N. Medical College, Belgaum.

You are requested to participate in a study which is an attempt to find out the efficacy of dressings with superoxidised solution as compared to dressings with povidine iodine in management of infected diabetic ulcers.

The diabetic ulcers are a common complication of diabetes mellitus and treatment of which is a major challenge. Presently these ulcers are being managed by local dressings with agents like Povidine Iodine, Eusol, etc… which have their own limitations. Superoxidised solution may represent an alternative to the currently available antiseptics and may answer the quest for better control of wound infection in diabetic patients. So, the study has been undertaken to compare the efficacy of dressings with superoxidised solution with povidine iodine in the management of infected diabetic ulcers.

This study will be conducted by Dr. ***** *******, Post Graduate in Department of Surgery, under the direct supervision and guidance of Dr. ***** *******, Professor, Department of Surgery, J. N. Medical College, Belgaum.

You need to be eligible, meeting all the selection criteria to participate in this study. You should be willing to provide information about yourself. Sixty subjects will be enrolled in this study that will then be randomized in either of 2 groups (details given below).

If you agree to participate in this study, you will be randomly allotted into a group (A or B) and accordingly receive either the standard management (dressing with povidine iodine) or the newer management (dressing with superoxidised solution). The ulcer size will be assessed once a week for two weeks for healing and control of infection. There is no observable risk associated with this study.

No financial incentives are being offered to enrolled subjects. It is purely being done with the idea of research purpose and all cost of the study will be borne by the investigator. In the event that you become injured as a result of taking part in this study, treatment will be offered to you at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, or you will be given information about where to receive medical care in which case you/your insurance company will be responsible for the costs. However, no reimbursement, compensation or free medical care will be given.

Every effort will be made to protect the confidentiality of the information you provide. Only Dr. ****** ******* and Dr. ****** ****** will have access to the information provided by you. Results of this study may be published but your identity will not be revealed. Taking part in this study is voluntary; you may choose not to enroll in this study. Your decision will not change the present or future health care services offered to you at KLES Dr. Prabhakar Hospital,

Belgaum. The alternative that you have is to undergo the traditional procedure that is carried out in KLES Hospital.

If you have any queries about the study, you may contact Co-investigator, Dr. ***** ******* (***** *******) / Dr. ***** ****** (***** ******) Professor, Department of Surgery, J. N. Medical College, Belgaum, without any hesitation. In case you need any further information regarding your rights as a study participant, you may contact Dr. **** ******, Chairman of Institutional Dissertation and Thesis Ethical Committee on human subject research on ***** *********.

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**

Annexures

Annexure II

ANNEXURE II – PROFORMA

I. PATIENT IDENFICIATION DATA

GROUP: CASE NO. :

I.P/ O.P.D NO.: D.O.A:

NAME: D.O.S:

AGE/ SEX: D.O.D:

OCCUPATION:

ADDRESS:

II. CHIEF COMPLAINTS:

III. MEDICAL HISTORY

Peripheral neuropathy : ( )

Nephropathy : ( )

Retinopathy : ( )

PVD : ( )

CVD : ( )

IV. DIABETIC STATUS

Type : Duration :

Medication :

Oral Hypoglycemics : ( )

Insulin : ( )

V. ULCER DETAIL

1. Mode of onset

Traumatic : ( )

Spontaneous : ( )

Pressure : ( )

Others : ( )

2. Duration :

3. Progress :

VI. WOUND OBSERVATIONS:

		Before dressing	**End of first week**	**End of second week**
1.	Site			
2.	Size			
3.	Shape			
4.	Edge			
5.	Margin			
6.	Floor			
7.	Base			
8.	Discharge			
9.	Surrounding Skin			
10.	Slough /necrotic tissue			

VII. NEUROLOGICAL EXAMINATION:

1) Motor System-

2) Sensory System-

VIII. VASCULAR EXAMINATION

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

IX. ANY FOOT DEFORMITY PRESENT

Toe deformity: ( )

Charcot's foot: ( )

Foot drop: ( )

X. IF DEBRIDEMENT HAS BEEN DONE

Specify, Date :

Side :

Type of anaesthesia :

No. of debridements :

XI. INVESTIGATIONS:

CBC : Hb- ( ) TLC- ( ) DC- (N- , L- , M- ,E-)

FBS: ( ) Date Time

Blood Urea ( )

Sr. Creatinine ( )

Urine:

Routine

Microscopy

X-ray

AP view

Lat. View

Tissue culture/ sensitivity

Before dressing:

10 days after dressing:

COLOUR DOPPLER:

Annexures

Annexure III

ANNEXURE III – PHOTOGRAPHS

Photograph 1: A. Ulcer before dressing. B. Decrease in ulcer size after dressing with superoxidised solution.

Photograph 2. Superoxidised solution

ANNEXURE IV - MASTER CHART - GROUP A

Serial number	In Patient Number	Sex	Age (Years)	DM status			Ulcer details						Tissue culture		Organism Isolated
				Type	Duration (Years)	Medication	Site	Purulent/ Serous Discharge	Initial Ulcer Area (mm2)	Final Ulcer Area in (mm2)	Change in Ulcer Area	% reduction in area	Before	After	
1	463304	M	36	2	3	I	RDF	P	3956	1560	2396	60.6	P	AB	PSEUDOMONAS
2	461940	M	69	2	25	I	RL	P	1789	666	1123	62.8	P	AB	PROTEUS
3	468140	F	47	2	13	I	LDF	P	4684	1741	2943	62.8	P	P	STREPTOCOCCUS
4	479521	M	75	2	33	O	LDF	P	2386	1024	1362	57.1	P	AB	PSEUDOMONAS
5	478429	M	65	2	28	O	RDF	P	5246	1865	3381	64.4	P	AB	E. COLI
6	478024	M	42	2	14	I	RS	P	840	256	584	69.5	P	AB	PSEUDOMONAS
7	479098	F	55	2	16	O	LS	P	2541	1055	1486	58.5	P	P	ACINOBACTER+E. COLI
8	480914	M	57	2	13	O	LDF	P	2112	1078	1034	49	P	P	E. COLI
9	483715	M	65	2	20	I	LS	P	3155	1413	1742	55.2	P	AB	ACINOBACTER
10	481669	M	76	2	15	I	RDF	P	2891	1204	1687	58.4	P	AB	E. COLI
11	484035	M	32	2	1	O	RDF	P	3561	1364	2197	61.7	P	AB	PSEUDOMONAS
12	463127	F	30	1	25	O	RDF	P	1348	431	917	68	P	P	E. COLI
13	479628	M	60	2	15	I	RL	P	7821	3278	4543	58.1	P	AB	STAPHYLOCOCCUS
14	486360	F	65	2	30	I	RS	P	1853	621	1232	66.5	P	AB	PSEUDOMONAS
15	456588	M	30	2	4	O	RS	P	3120	1278	1842	59	P	P	ACINOBACTER
16	483449	M	62	2	17	I	RDF	P	2115	715	1400	66.2	P	AB	E. COLI
17	467425	M	77	2	35	I	LDF	P	5456	2564	2892	53	P	AB	E. COLI
18	471519	M	75	2	29	O	LL	P	2561	955	1606	62.7	P	AB	KLEBSIELLA
19	477659	M	64	2	15	O	RL	P	4387	2015	2372	54.1	P	P	PROTEUS
20	477629	F	52	2	12	O	LDF	P	3812	1321	2491	65.3	P	AB	PSEUDOMONAS
21	478752	M	35	2	3	O	LS	P	4536	2045	2491	54.9	P	AB	STREPTOCOCCUS
22	491402	M	47	2	15	O	RDF	P	7659	2999	4660	60.8	P	AB	STREPTOCOCCUS
23	494546	F	71	2	32	I	RS	P	1948	862	1086	55.7	P	P	E. COLI + PROTEUS
24	473047	M	54	2	16	I	RS	P	5762	2738	3024	52.5	P	AB	E. COLI
25	484395	M	53	2	11	O	RDF	P	3150	1389	1761	55.9	P	AB	PSEUDOMONAS
26	498747	M	56	2	10	O	RL	P	6754	2915	3839	56.8	P	AB	E.COLI
27	500059	M	60	2	21	O	RGR	P	5131	2406	2725	53.1	P	AB	PROTEUS
28	497566	M	56	2	18	I	LS	P	7254	3451	3803	52.4	P	AB	ACINOBACTER
29	490586	F	70	2	29	O	LDF	P	3878	1754	2124	54.8	P	P	PSEUDOMONAS
30	485440	M	41	2	8	O	RDF	P	2969	1247	1722	58	P	AB	KLEBSIELLA

ANNEXURE IV - MASTER CHART - GROUP B

Serial number	In Patient Number	Sex	Age (Years)	DM status			Ulcer details						Tissue culture		Organism Isolated
				Type	Duration (Years)	Medication	Site	Purulent/ Serous Discharge	Initial Ulcer Area (mm2)	Final Ulcer Area in (mm2)	Change in Ulcer Area	% reduction in area	Before	After	
1	466074	F	35	2	7	O	LS	P	6358	3990	2368	37.2	P	P	E.COLI
2	469267	F	54	2	22	O	RL	P	2018	1496	522	25.9	P	AB	STAPHYLOCOCCUS
3	470437	F	19	1	15	I	RL	P	2808	1912	896	31.9	P	P	KLEBSIALLA + E.COLI
4	476722	M	42	2	12	O	LS	P	4150	3108	1042	25.1	P	P	STAPHYLOCOCCUS
5	479429	M	35	2	2	O	RT	P	7587	5246	2341	30.9	P	P	PROTEUS
6	477429	M	48	2	15	I	RL	P	3522	2315	1207	34.3	P	AB	E.COLI
7	479046	M	60	2	26	O	RS	P	7120	4312	2808	39.4	P	AB	PROTEUS
8	479622	F	65	2	23	I	LT	P	1824	1294	530	29.1	P	P	PSEUDOMONAS
9	482432	M	75	2	34	I	LDF	P	1245	700	545	43.8	P	AB	STAPH + PSEUDOMONAS
10	481843	F	64	2	21	I	LDF	P	8600	5220	3380	39.3	P	AB	STREPTOCOCCUS
11	484395	M	53	2	11	I	RS	P	1044	606	438	42	P	P	PROTEUS
12	481167	M	56	2	19	O	RS	P	948	699	249	26.3	P	AB	KLEBSIALLA
13	484911	M	47	2	10	O	RS	P	3251	1925	1326	40.8	P	AB	PSEUDOMONAS
14	465108	M	66	2	23	I	LDF	P	3847	2214	1623	42.4	P	AB	STAPHYLOCOCCUS
15	485951	M	55	2	15	O	RDF	P	4522	2112	2410	53.3	P	P	KLEBSIALLA+E.COLI
16	472659	M	52	2	13	O	RS	P	2913	1914	999	34.3	P	P	PROTEUS
17	480064	M	56	2	11	O	RDF	P	5440	2994	2446	45	P	AB	STREPTOCOCCUS
18	478853	M	80	2	19	I	RGR	P	5930	3105	2825	47.6	P	P	STAPHLOCOCCUS
19	468405	M	55	2	21	I	RS	P	2619	1515	1104	42.2	P	P	PSEUDOMONAS
20	477569	M	55	2	21	O	RDF	P	4890	2712	2178	44.5	P	AB	STAPHYLOCOCCUS
21	478800	F	45	2	12	O	RS	P	5125	3126	1999	39	P	AB	E.COLI
22	478685	M	46	2	9	O	LGR	P	1964	823	1141	58.1	P	P	PROTEUS
23	485585	F	46	2	7	O	LDF	P	3016	1816	1200	39.8	P	AB	STAPHYLOCOCCUS
24	485462	M	71	2	27	I	RDF	P	4478	2498	1980	44.2	P	AB	E.COLI
25	492620	M	45	2	17	O	LDF	P	4915	2715	2200	44.8	P	P	PSEUDOMONAS
26	494111	M	52	2	13	I	LL	P	2417	1268	1149	47.5	P	AB	STAPHYLOCOCCUS
27	502869	M	42	2	10	I	LDF	P	6258	3194	3064	49	P	AB	PSEUDOMONAS
28	487427	M	56	2	17	I	LS	P	1914	812	1102	57.6	P	P	E.COLI
29	453616	M	44	2	10	O	LS	P	4861	2941	1920	39.5	P	P	STREPTOCOCCUS
30	472664	M	28	1	25	O	LDF	P	4187	1962	2225	53.1	P	P	STAPHYLOCOCCUS

Annexures

Annexure IV

ANNEXURE IV – KEY TO MASTER CHART

AB	-	Absent
E. Coli	-	Escherichia coli
F	-	Female
I	-	Insulin
LDF	-	Left dorsum of foot
LGR	-	Left gluteal region
LL	-	Left leg
LS	-	Left sole
LT	-	Left thigh
M	-	Male
mm	-	Millimeters
O	-	Oral
P	-	Present
RDF	-	Right dorsum of foot
RGR	-	Right gluteal region
RL	-	Right leg
RS	-	Right sole
RT	-	Right thigh