"COMPARATIVE STUDY OF EFFECT OF TOPICAL PHENYTOIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A RANDOMIZED CONTROL STUDY"

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Endorsement by the Hod/Principal/ Head of the Institution

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF EFFECT OF TOPICAL PHENYTOIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A RANDOMIZED CONTROL STUDY"** is a bonafide research work done by **Registration No. BH0109004.**

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LIST OF ABBREVIATIONS USED

DF	-	Degree of freedom
DM	-	Diabetes mellitus
ECM	-	Extra cellular matrix
EGF	-	Endothelial derived growth factor
ER	-	Endoplasmic reticulum
HCD	-	Hydrocolloid
MM	-	Millimeter
MMP	-	Matrix metalloproteinase
PDGF	-	Platelet derived growth factor
SD	-	Standard deviation
IP. NO.	:	Inpatient Number
DOA	:	Date of Admission
DOD	:	Date of Discharge
Hb	:	Haemoglobin
PCV	:	Packed Cell Volume
RBS	:	Random Blood Sugar
C/S	:	Culture and sensitivity

ABSTRACT

Background and objectives

The management of wound and wound dressing is an important aspect of chronic ulcer management. Choosing an appropriate dressing can be a complex process. Topical phenytoin helps in faster wound remodelling.

Objective

The objective of the study was to assess the effect of topical phenytoin dressings with normal saline dressing in healing of diabetic foot ulcers in terms of mean decrease in size of the ulcer

Methodology

The present one year randomized controlled trial was conducted in the Department of Surgery, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 60 patients with diabetic foot ulcer during the period of January 2010 to December 2010. The patients were divided into two different groups by number randomization (Group 1 topical phenytoin and Group 2 normal saline dressing). Wound measurement was taken on day one and end of every week for four weeks. Mean reduction in ulcer area at the end of four weeks was calculated.

Results

There was no statistical difference in the baseline characteristics like age, sex and initial wound area of the ulcer between the two groups. The mean reduction in wound area was 1856.9±724.9mm in patients treated with topical phenytoin dressings and1066.8±565.3mm in patients treated with normal saline dressings, which is statistically significant ($p<0.001$).

Conclusions

Topical phenytoin dressing can be used for the healing of diabetic foot ulcer

Key word

Diabetic ulcers; topical phenytoin; normal saline dressing; Wound area

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INTRODUCTION

Chronic wounds, especially non healing types, are one of the most common surgical conditions a surgeon comes across. One of the most feared complication of long term diabetes is loss of leg or foot. It has been estimated that one in five of all diabetic admissions to hospitals are for foot ulcers[1]. From time immemorial doctors have been trying many methods to treat these types of wounds.

The diabetic foot ulcers arrest in inflammatory stage of healing due to neuropathy, angiopathy and infections. Risk of lower extremity amputation is 15 fold higher in diabetics than non diabetics. 15% of all the diabetics develop diabetic ulcer and the commonest site being the foot[2] .Treatment of these diabetic feet is a major problem. The quest for better wound healing is one of the oldest challenge for the medical practice.

The management of wound and wound dressing is an important aspect of diabetic ulcer management, which is neglected many a time. Care of the wound involves management of the ulcer, care of the exudates and knowledge and rational use of myriad dressing materials.

Basic requirements of the ideal ulcer dressing[3];

- Maintain high humidity between wound and dressing.
- Absorbent, removes excess exudates.
- Non-adherent, allowing easy removal without trauma at dressing change.
- Safe and acceptable to patient (non-allergic).
- Permit gaseous exchange but impermeable to micro-organism.
- Cost-effective.

During the last two decades a wide variety of innovative dressings have been introduced.

Cost-effective Treatment plan for diabetic foot includes surgical debridement of wound, improvement of circulation through surgery or therapy, special dressing and antibiotics. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings. Topical antiseptic, such as povidine-iodine are usually considered to be toxic to healing wounds

Diabetic ulcers are the indication for 50% of non traumatic amputations. There is a need for evaluation of new method for treating these ulcers which are economical and more effective in increasing healing rate and decreasing the amputation rate. Some studies on topical phenytoin have shown increased healing rate in chronic foot ulcers than other conventional dressings[4,5,6,7,8,9].

Few studies stated that topical phenytoin increased the healing rate of diabetic foot ulcers between 3rd and 4th week, but there was no difference in complete healing of the ulcers compared to other conventional dressings.[4,5]

Phenytoin acts by stimulating fibroblasts enhancing granulation tissue formation, decreasing collagenase activity.[6] Systemic absorption of phenytoin on topical use in diabetic ulcer was not significant. Other side effects noticed on use of topical phenytoin in diabetic ulcer were transient burning sensation initially and hypergranulation.[5,6,7,8]

Though many studies are conducted on using topical phenytoin in chronic leg ulcers only few studies are conducted on diabetic ulcers and such studies have not been conducted in our institute.

OBJECTIVE OF THE STUDY

To evaluate the effect of topical phenytoin dressing with Normal Saline dressing in healing of Diabetic foot ulcers.

REVIEW OF LITERATURE

CHRONIC FOOT ULCERS

Acute ulcers are sometimes defined as those that follow the normal phases of healing; they are expected to show signs of healing in less than 4 weeks and include traumatic and postoperative wounds.

Chronic ulcers are those that persist for longer than 4 weeks and are often of complex poorly understood origin.

Chronic leg ulceration affects about 1% of the middle-aged and elderly population. It most commonly occurs after a minor injury in association with:

- Chronic venous insufficiency (45-80%)
- Chronic arterial insufficiency (5-20%)
- Diabetes (15-25%)

Chronic leg ulcers may also be due to skin cancer, which may be diagnosed by a skin biopsy of the edge of a suspicious lesion. There are also many less common causes of ulcers including systemic diseases such as systemic sclerosis, vasculitis and various skin conditions especially pyoderma gangrenosum.

Causes of formation of chronic foot ulcer

- Recurrent infection
- Trauma
- Absence of rest
- Poor blood supply
- Hypoxia
- Oedema of the area
- Loss of sensation

DIABETES MELLITUS

Definition

"Diabetes mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrates, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both".[10-16]

Classification[10-16]

Type I

Type Pathology

IA : Autoimmune beta cell destruction which leads to insulin deficiency.

IB : Lack of immunologic markers indicative of an autoimmune destructive process of the beta cells..

Type II

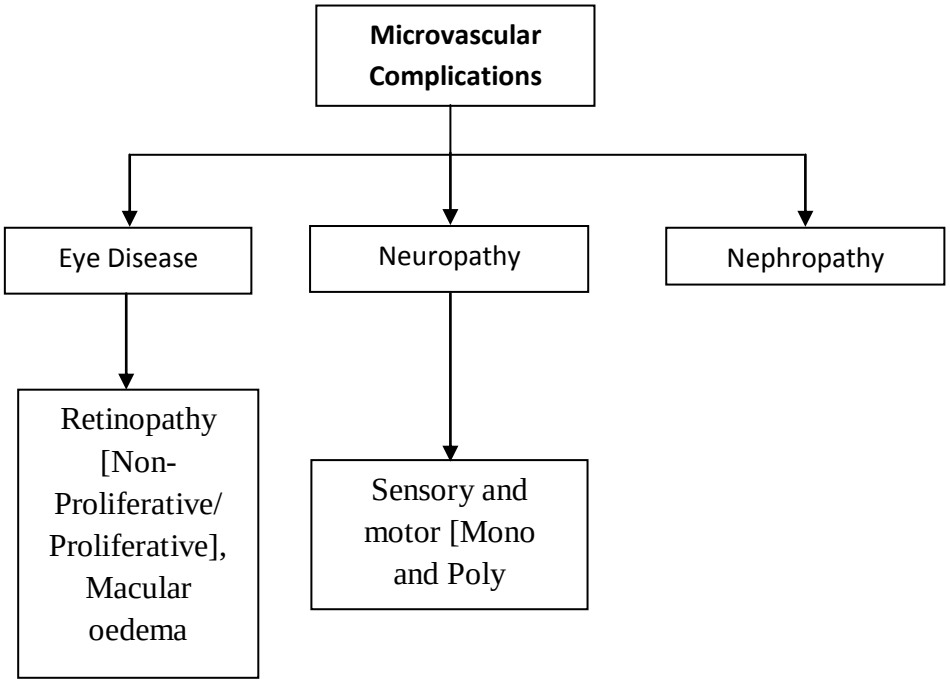
It is a heterogeneous group of disorders characterized by:-

- Impaired insulin secretion.
- Variable degree of insulin resistance.
- Increased glucose production

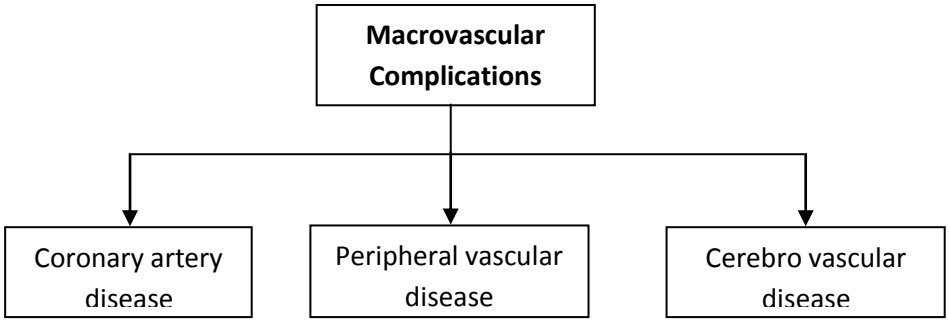
Chronic Complications of Diabetes Mellitus[10-16]

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and morality associated with the disease.

Microvascular complications in diabetes mellitus



Macrovascular complications in diabetes mellitus



Other complications

- Gastro-intestinal [Gastropareasis, diarrhea]
- Genitor-urinary [Uropathy / Sexual dysfunction]
- Dermatologic
- Infections
- Cataracts and Galucoma

Microvascular complications of both type 1 and type 2 diabetes mellitus results from chronic hyperglycemia.

Lower Extremity Complications and diabetes mellitus[10-16]

- Foot ulcers and infections are a major source of morbidity in individuals with DM.
- The reasons for the increased incidence of these disorders in DM involve the interaction of several pathogenic factors:
    - Neuropathy.
    - Peripheral arterial disease.
    - Abnormal foot biomechanics.

Neuropathy

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

Peripheral sensory neuropathy

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

Motor and sensory neuropathy

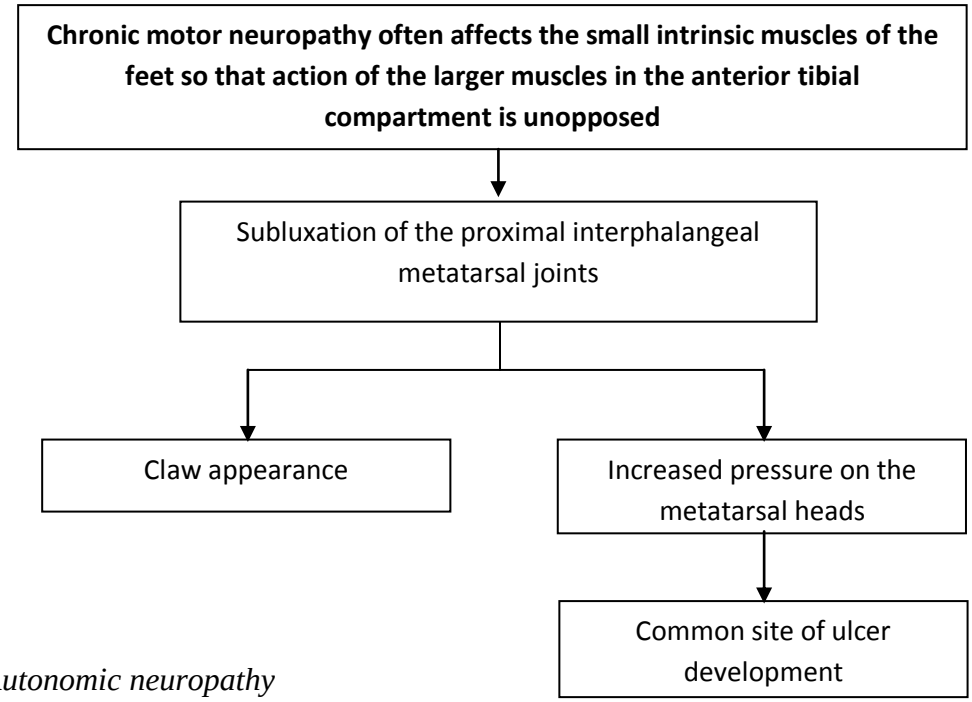
Lead to abnormal foot muscle mechanics and to structural changes in the foot [hammer toe, claw toe deformity, prominent metatarsal heads, Charcot arthropathy].

Charcot arthropathy (Diabetic neurpathic arthropathy):

It is characterized by collapse of the arch of the mid foot and bony prominences in peculiar places. It is caused by triad of;

a. Small muscle wasting.
b. Decreased sensation.
c. Abnormal distribution of weight when standing.

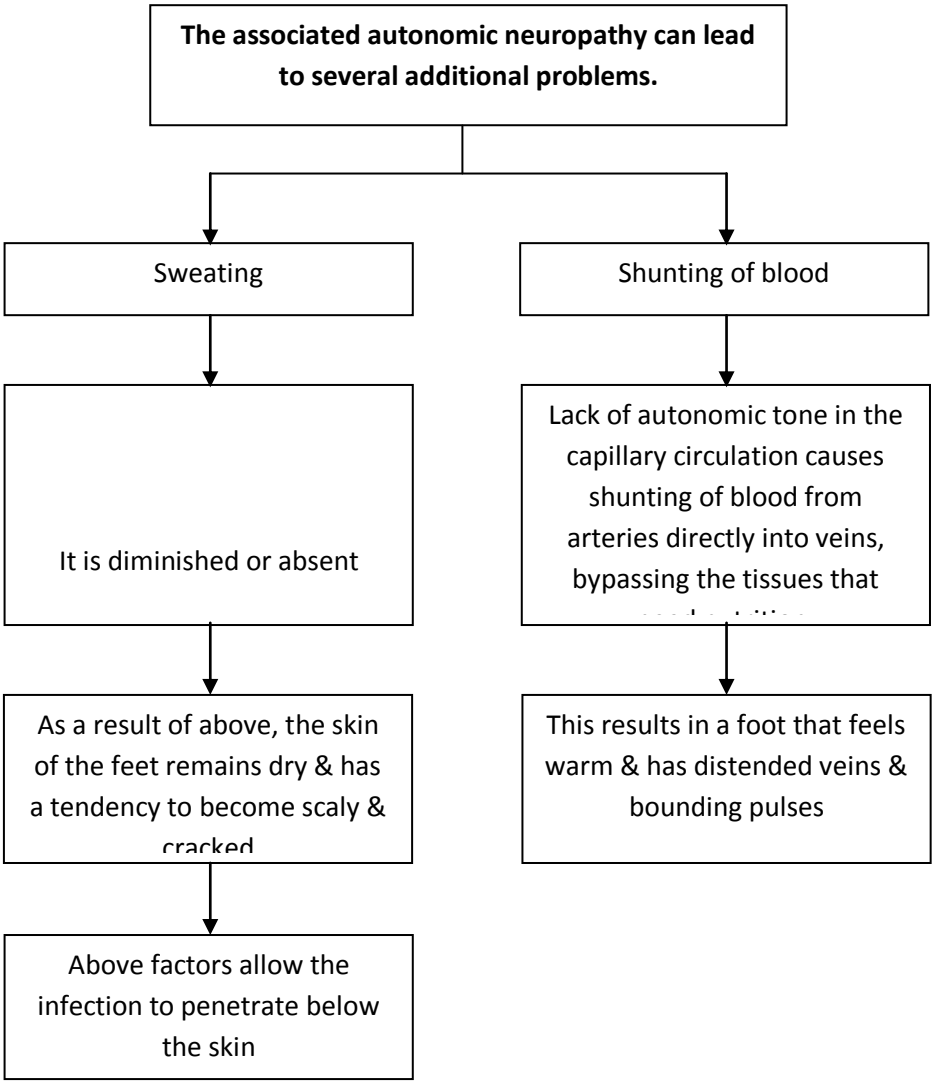
Pathophysiology of Charcot arthropathy



Autonomic neuropathy

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

Pathophysiology of Autonomic Neuropathy in Diabetes Mellitus



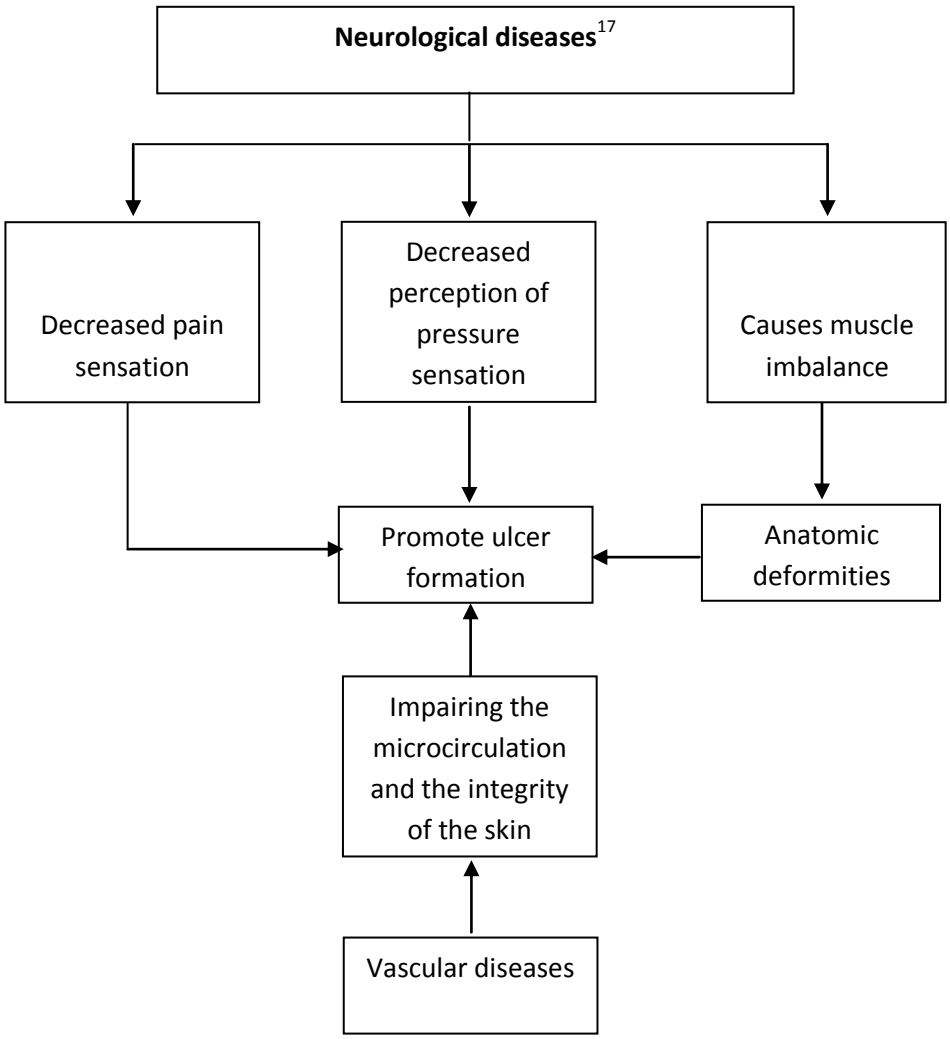
Peripheral arterial disease and poor wound healing

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. It impedes resolution of minor breaks in the skin of the lower limb, allowing them to enlarge and to become infected.

Abnormal foot biomechanics

Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulceration.

Pathogenesis of diabetic foot



Changes in foot caused by diabetes

1. Dryness of skin and callus formation due to peripheral neuropathy.
2. High pressure at bony prominences due to;
    - Decrease plantar tissue thickness
    - Weak intrinsic muscles of foot
    - Imbalances of flexors and extensors causing clawing of foot
    - Pulling away fat padding from metatarsal heads.

3. Limited joint mobility due to;
    - Collagen abnormality
    - Thickening of skin tendons and joint capsule
    - Decreased tissue flexibility
    - Increased plantar pressure

Recommendations[18]

- The feet should be examined at least annually in patients with Type-2 diabetes and in those with Type-1 diabetes for more than five years.
- A detailed neurological examination and assessment for Peripheral vascular disease should be performed.
- We recommend using the quantitative foot assessment for neurologic symptoms.
- Patients should be considered at particularly high risk for future plantar ulceration if they have[19]
    - A Previous history of foot ulceration or amputation.
    - Neuropathic foot deformities, especially with overlying bunions or calluses.

Prophylactic foot care

It is important that prophylactic advice on foot care be given to any patient whose feet are at high risk. The recommendations for prophylactic foot care are.

Avoid:

- Smoking
- Walking barefoot
- The use of heating pads or hot water bottles
- Stepping into a bath without checking the temperature.

The feet should be:

- Washed daily in tepid water.
- Mild soap should be used and the feet should be dried by gentle patting.
- A moisturizing cream or lotion should then be applied.

Toe Nails:

The toe mails should be:

- Trimmed to the shape of the toe
- Filed to remove sharp edges.

Shoes:

- The patient's shoes should be snug, not tight,
- Patients who have misshapen feet or have had a previous foot ulcer may benefit from the use of special customized shoes.

Socks:

Socks should be

- Cotton
- Loose fitting
- Should be changed every day

Inspection of feet:

- The feet should be inspected daily. Looking between and underneath the toes and at pressure areas for skin breaks, blisters, swelling, or redness. The patient may need to use a mirror or, if vision is impaired, have someone else perform the examination.

Examination of foot by medical person:

- A particularly effective strategy is to make specific recommendations to the patient in the form of a 'contract' and to advise the patient to request that his or her feet be examined at every visit to the doctor or nurse.[20]

Risk factors for foot ulcers or amputation

- Male sex
- Diabetes> 10 years duration
- Peripheral neuropathy [10-16,21,22]
- Abnormal structure of foot [bony abnormalities, callus, thickened nails]
- Peripheral arterial disease
- Smoking
- History of previous ulcer or amputation.[10-16,21,22]
- Poor glycemic control. [10-16,21,22]

ULCER

Definition

An ulcer is defined as break in the continuity of an epithelial surface, characterised by progressive destruction of the surface epithelium.

Acute wound

It is defined as the traumatic loss of normal structure and function to recently uninjured tissue after a noxious insult.[23]

Chronic wound

Wounds more than or equal to four weeks duration, is known as chronic wounds. Disruption in the event of healing regulated by process of cellular, humoral ,

and molecular events and resulting in a time dependent but predictable and orderly pattern of tissue repair.[24]

Characteristics of chronic wound

Floor is covered with pale granulation tissue, scanty discharge indurated base, edge and surrounding skin.

WOUND HEALING

Historical background

- Wounds were probably earliest problems of human race.
- Early surgeons like Ambrose Pare, John Hunter and Sir James Paget have given some scientific knowledge to their handling of wounds, particularly those resulted from war.[25]
- Halsted was intensely interested in wound healing process.
- In the early 1900's Carrel and his associates made investigation with the scientific approach to wound healing. Later Carrel (1916), Harvey and Howe's (1930), studied incised wounds and contributed to the knowledge of wound healing.[26]

Definition

"Body replacement of destroyed tissue by the living tissue" or "Integrated series of cellular and biochemical events which restores the functional integrity and regains the strength of injured tissue".

Phases of healing

Wound healing and repair are complex processes that involve dynamic series of events.

Coagulation

- Helps in preventing blood loss, covering wound surface and holding the wound edges together and thus contributing to the healing process
- Ross (1980) and Knighton et al (1982) have shown equivocally that fibrin and platelates play an important role in initiating the wound healing.

Granulation phase of wound healing

Granulation tissue[25]

"This is a highly vascular tissue, contains largely of;

1. Fibroblast.
2. Endothelial cells lining capillaries of newly spouting blood vessels.
3. Macrophages.
4. Pleuripotent pericytes.

Above all are embedded in a matrix consisting.

1. Fibronectin
2. Proteoglycans rich in Hyaluronicacid and collagen [This collagen is at first mainly of Type-III, changing later to Type I].

Functions

- Fill the gap of the wound
- Supports the growing and migrating epithelial cells – The connective tissue matrix of granulation tissue forms nutritive substrate, over which regenerating epidermis can migrate and is gradually replaced by scar tissue.

Imporant factors for granulation tissue formation

- Chemotactic factor.
- Growth factor.
- Structural molecules.
- Proteases [Digests connective tissue matrix].

Angiogenesis or neo-vascularisation

It is a vital part of proliferative phase of wound healing and repair.[27]

Without angiogenesis**,** invasion of the wound bed by macrophages and fibroblasts would cease due to lack of oxygen and nutrients.[27]

In the initial stages, these vessels lack basement membrane and have loose cellular junction and are fragile in nature. Due to this, on slightest touch, the vessels bleed profusely which is a characteristic feature of newly formed capillaries. The leakage facilitates the movement of cells and macromolecules into wound site.[27]

There are four steps in angiogenesis:[26,27]

- *Step-1* Proteolytic degradation of basement membrane of parent vessel is to allow formation of capillary sprout and subsequent cell migration.[27] Angiogenic factors acts on capillary endothelial cells, which releases collagenase. This enzyme degrades the collagen of basement membrane.[26]
- *Step-2* Fragmentation of the collagen of basement membrane, permits the migration of endothelial cells into peri-vascular spaces.[13]
- *Step-3* Endothelial cells migrate into the peri-vascular spaces where they form buds.[27]
- *Step-4* Maturation of endothelial cells and organisation into capillary loops**.**

- Functional capillary loops: During dermal repair, these buds grow rapidly towards the free surface, where they branch at their tips and unite to form **functional capillary loops**.
- Superficial capillary plexus: On these loops, new buds develop, so that, a **superficial capillary plexus** rapidly forms in the granulation tissue.
- Canalization: Proliferation and branching of cords of endothelial cells later become canalized to form growing capillary buds of healing wound.
- Fusion: Capillaries originating from opposite sides of the wound fuse and establish a complete circulation within the wound.

Remodelling of the vasculature

There is constant remodelling of the vasculature, which involves obliteration of many of the capillaries.

As each capillary loop becomes functional, it brings nutrient and oxygen to nearby cells, enabling the fibroblast to secrete materials for the matrix, through which macrophages and other cells can migrate further.

As the scar maturation proceeds, capillaries gradually regress and the red vascular rich wound tissue transforms into a white, relatively avascular poor scar.

The above proliferative and migratory processes are repeated sequentially, until wound bed is filled with granulation tissue.

Macrophagia[27]

- It is the point at which protecting and clearing functions of inflammatory response are linked to starting of reparatory process

Macrophagia is;

1. Migration of Monocyte [from blood] to tissue injury site.
2. Conversion of monocyte to Macrophage after migration to tissue injury site.
    - They are key cells in dermal repair
    - Wound macrophages, which appear subsequent to the cells, play pivotal role in healing by liberating various factors.

Functions of macrophages[28]

- Take over the function of phagocytes that is debridement.
- Release matrix metalloproteinases (MMP).
- Macrophages secrete numerous cytokines.
- Macrophages also release growth factors that stimulate fibroblast, endothelial cells and keratinocyte proliferation.
- Promote angiogenesis by liberating endothelial growth factor [EGF].
- Macrophage-secreted platelet derived growth factor (PDGF) stimulate collagen and proteoglycan synthesis.

Fibroplasia[28]

After injury, the normally and sparse fibroblasts are chemoattracted to the inflammatory site, where they divide and produce the components of the extra cellular matrix (ECM). After stimulation by macrophage- and platelate-derived cytokines and growth factors, the fibroblast which is normally arrested in G_0 phase, undergoes replication and proliferation.

The primary function of fibroblsts is to synthesize collagen. The rate of collagen synthesis declines after 4 weeks and eventually balances the rate of collagen

destruction by collagenase (MMP-1). At this point the wound enters a phase of collagen maturation. The maturation phase continues for months or even years.

Collagen

Structure[28]

The proline- and glycine- rich collagen molecule is a long, stiff, triple-stranded helical structure that consists of three collagen polypeptide α chains twist around one another in a ropelike superhelix. With its ringlike structure, proline provides stability to the helical conformation in each α chain, whereas glycine, because of its small size, allows tight packing of the three α chains to form the final superhelix. There are at least 20 types of collagen, the main constituents of connective tissue being types I, II, III,V, IX. In early wound healing there is increased expression of type III collagen.

Collagen synthesis[28]

Collagen polypeptide chains are synthesized on membrane-bound ribosomes and enter the endoplasmic reticulum (ER) lumen as pro-α chains. Within the lumen of the ER, some of the prolines and lysines undergo hydroxylation to form hydroxyproline and hydroxylysine. Hydroxylation results in the stable triple-stranded helix through the formation of interchain hydrogen bonds. The pro-α chain then combines with two others to form procollagen, a hydrogen-bonded, triple-stranded helical molecule. After secretion into the ECM, specific proteases cleave the propeptides of procollagen molecule to form collagen monomer. These monomers assemble to form collagen fibrils in the ECM.

Functions

a) Collagen is essentially a product of fibroblast.
b) Collagen is the most abundant proteins of the connective tissue.
c) Supports to the tissues
d) Provides structural framework to other types of tissues.
e) Acts as a medium where blood vessels and nerves are passing.
f) Brings and keeps the wound edges together and provides tensile strength for holding together – this holding strength prevents the breakdown of tissue (organ) at the healed site.
g) Fill the gap caused by the tissue loss.

Ground substance in healing wound[28]

- Connective tissue consists of cellular and non cellular (matrix). Matrix is again composed of fibres and ground substance.
- **Ground substance** is non-fibrous part of the matrix in which cells and fibres are embedded.
- **Consistency:** Except in mineralized connective tissue, the ground substance is viscous gel.

Constituents

- Water (High proportion).
- Mucopolysaccharides.
- Fibronectin.
- Chondronectin.
- Mucoproteins.

- Glycoproteins.
- Lamenin.
- Entactin.

Wound contraction[28]

- **Definition:** "Wound contraction may be defined as a process by which the size of full thickness open wound is diminished by centripetal movement of the thickness of surrounding skin".
- The feature that most clearly differentiates primary from secondary healing is the phenomenon of wound contraction, which occurs in large surface wounds.
- Wound contraction is one function of granulation tissue which is critical for repair.
- The events of wound healing from injury to fibroplasia, occur in all wounds. But certain events like wound contraction occurs characteristically in dermal wound.
- In humans, the wound contraction is less because in most part of the body the skin is somewhat firmly attached to subcutaneous tissue but it can occur in ares like back of neck and buttocks.

Timing

Wound contraction starts from about third or fourth day of healing and continues upto 15^{th} or 16^{th} day and stops thereafter, irrespective of whether the wound is totally closed or not.

Rate

- The rate of wound contraction is about 0.60 - 0.75 mm /day.
- Wound contraction is not materially affected by size or shape of the wound but perhaps by the length of the wound perimeter.

Mechanism

- The mechanism of wound contraction is disputable and debatable. Many theory like Pull theory, Push theory / Picture Frame theory etc. have been proposed but none of them appears to be satisfactory.
- Modified fibroblasts rich in actin filaments are responsible for wound contraction.
- Myofibroblasts are situated just under the advancing edges of the wound.
- In early phases of wound contraction, contractile epidermal cells in wound edges are suggested as a source of force.
- Wound contraction can be both beneficial or detrimental. Wound contraction can lead to distortion, disfigurement and impairment of function.

Epithelization

Definition

- Epithelization is a process of wound healing involving body surface.
- Unlike healing by fibroplasia where lost parenchymal cells are replaced by non-specific connective tissue, in epithelialisation lost epithelial cells are replaced by epithelial cells only. It is an example of healing by regeneration.

Stages

a) Mobilization and loosening of basal cells from their dermal attachment.

b) Migration or movement of cells to a position of cell deficit.

c) Proliferation or replacement of cells to a position of cell deficit and

d) Differentiation or restoration of cellular function.

Epithelization which depends on several factors;

- Size of wound.
- Location of wound.
- Shape of wound.
- Impairment of blood supply.
- Pathological modification of wound

Healing by epithelisation occurs in;

- Dermal wounds.
- Wounds of tracheobronchial surface.
- Surface wounds in gut, urinary bladder, uterus etc.

Timing

First 24 hrs of injury: Changes in epidermis leading to re-epithelization begin within 24 hours of the formation of a cutaneous wound.

Types of wound healing[28]

Healing by first intention

The wounds are sealed immediately with simple suturing, skin graft placement, or flap closure, such as closure of the wound at the end of surgical procedure.

Healing by secondary intention

No active intent to seal the wound. Generally, this type of repair is associated with a highly contaminated wound and will close by re-epithelialization, which results in contraction of the wound.

Heeling by tertiary intention

It is also referred to as delayed primary closure. A contaminated wound in initially treated by repeated debridement, systemic or topical antibiotics, or negative pressure wound therapy for several days to control infection. Once the wound is assessed as being ready for closure, surgical intervention, such as suturing skin graft placement, or flap design is performed.

MANAGEMENT OF CHRONIC WOUNDS

Wound dressings have been used since antiquity to facilitate the healing process. A material which when applied to the surface of a wound, provides and maintains an environment in which healing can take place at maximum rate; Thomas (1986).[29] The first antiseptic dressing was introduced by Lister in 1867 who soaked the lint and gauze in carbolic acid.[30]

Dressings used in chronic foot ulcer

Conventional dressings, such as gauze, impregnated gauze, gauze and cotton, packing strips have been in use for over fifty years.

Action of saline dressing

Normal saline dressing keeps the environment moist for proper healing. Normal saline dressing acts as an osmotic dressing, with time the concentration of the saline increases due to evaporation altering it from isotonic to hypertonic dressing

which in turn decreases evaporation of fluid from the wound, keeping it moist.[31]

Moist wound environment that these dressings provide are best for wound regeneration and repair and increasing the velocity of healing. Effective wound management aims to strike a balance that is a moist environment to promote healing, but not so wet as to cause maceration and excoriation.

Two factors are important for natural wound healing. One is wound exudates which is generic term given to liquid produced from wounds. Exudate keeps the wound moist, supplies nutrients, and provides the medium for migration and mitosis of epithelial cells. This in turn, keeps the wound supplied with leucocytes, helping to control micro organism. Second factor is the presence of white cells in the wound. White cells play a major role in wound healing by cleaning the wound, remove potentially pathogenic micro organisms and producing collagen, the building block of new tissue. Excessive exudates can cause maceration and hence the dressing should be able to absorb excessive exudates from the wound.[32]

Basic requirements of the ideal ulcer dressing[3]

- Maintain high humidity between wound and dressing
- Absorbent, removes excess exudates
- Non-adherent, allowing easy removal without trauma at dressing change
- Safe and acceptable to patient(non-allergic)
- Permit gaseous exchange but impermeable to micro-organism
- Cost-effective

Newer dressings available for diabetic ulcer

A wide variety of new dressing materials have been developed. However none of the newer dressing fulfill all the characteristics of an ideal dressings.

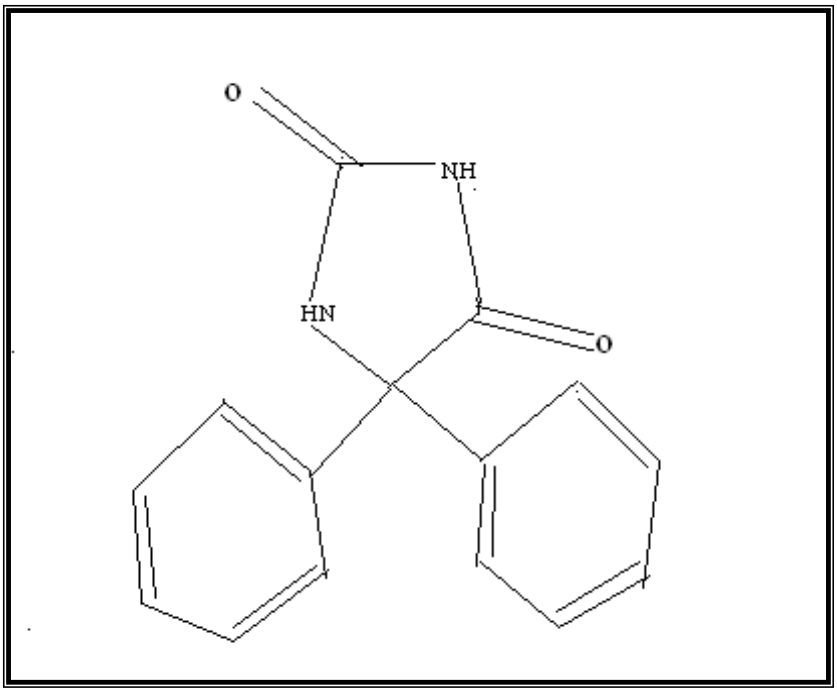
- Film dressing.
- Foam dressing.
- Nonadherent dressing (Paraffin-impregnated tulle dressing).
- Hydrogels.
- Hydrocolloids.
- Alginates.

Newer therapies available for diabetic ulcer

- Plate derived growth factors.
- Demagraft.
- Apligraf.
- Granulocyte-colony stimulating factor.
- L-lysine

TOPICAL PHENYTOIN

Chemical structure of phenytoin



In 1938, Meritt and Putnam published their note worthy. Data using phenytoin to treat major, absence and psychic equivalent seizures. Since that time phenytoin has been considered highly effective anticonvulsant . Even decades later it continues to be a highly effective anticonvulsant and ant arrhythmic .[33]

Phenytoin is type 1B anti arrhythmic and also used in treatment of trigeminal neuralgia Phenytoin has been used to treat ulcers epidermolysis bullosa and inflammatory condition. Numerous allergy and proliferate, idiosyncratic cutaneous side effects have been reported with its use.[34] A frequent observed and unwanted side effect of phenytoin, is gingival hyperplasia, specially in children

This side effect suggested that phenytoin can induce the growth of connective tissue, and may have the ability to promote wound healing. The beneficial effect of phenytoin In wound healing had been reported in 1945 and was observed in the first clinical trial for gingival wounds in 1958. Since then, the effectiveness of topical phenytoin has been confirmed by several clinical trials for different types of wounds.

Postulated Mechanisms of Action

Wound healing is a complicated process requiring the collaboration of many groups of cells and the mechanism by which phenytoin promotes wound healing is not fully understood, but several theories have been proposed.

Phenytoin wound healing mechanisms may include[35,36] :

1. Stimulation of fibroblast proliferation.
3. Enhancing the formation of granulation tissue.
4. Decreasing collagenase activity, inhibition of glucocorticoid activity
5. Direct or indirect antibacterial activity by affecting inflammatory cells
6. Phenytoin increases gene expression of the platelet derived growth factor p chain in macrophage and monocytes.

Clinical Experience

War and Non-War Wounds

One open trial evaluated 19 patients with missile wounds and 6 patients with refractory ulcers.[37] All wounds were debrided if needed and the wounds were cleansed with normal saline, dried, and covered with a thin layer of phenytoin sodium powder on a daily basis and the course of treatment ranged from 2 to 4 weeks. 22 of 25 patients had complete wound healing. Mean healing time for the missile wounds was 2 weeks, compared to 6-8 weeks for historical controls. The healing time for patients with refractory wounds was 4 weeks.

Burns

In a study reported by Lodha[38] two burn surfaces were evaluated for each of 50 patients with second-and third-degree burns. One burn surface on each patient was dressed with either 1 % silver sulfadiazine cream or with a thin layer of phenytoin powder. At 20 days, the burn area was reduced by 89.6% for the phenytoin group compared to 56.9% for the silver sulfadiazine group ($p<0.001$). Grafting was 100% successful for phenytoin treated sites versus 70% of the sites treated with silver sulfadiazine.

Second and third degree burn wounds were also treated with phenytoin and compared to silver sulfadiazine cream. In second degree burns, the percentage of reduction in mean burn area was 89.6% for phenytoin sites versus 56.9% for the silver sulfadiazine treated wounds ($p=<0.001$)[39]

Abscess Cavities

Forty patients with gluteal abscess secondary to intramuscular injections were studied by Lodha et al[40]. Twenty patients were assigned to receive topical phenytoin and a dry dressing. The 20 control cases were first treated with 15% Eusol

(chlorinated lime and boric acid). The cavities were then washed with 4% urea and dressed with normal saline. The mean rate of reduction of wound area was significantly better for the phenytoin group compared to the control group on day 10 ($p<0.05$ %) and day 20 ($p<0.01$%). The mean volume reduction rates were also better for phenytoin group compared to control group on day 10 and day 20 ($p<0.005$%). By day 20, 17 patients of the phenytoin group had treated completely, compared with only 1 in the control group.

Diabetic Foot Ulcers

A prospective, controlled trial examined the use of topical phenytoin versus control therapy in 100 non-insulin dependent diabetic patients with foot ulcers[41]. In the control group (n=50), a sterile occlusive dressing was applied daily. In the phenytoin group (n=50), phenytoin powder was applied in a "thin layer" to the ulcer surface, then dry dressing daily. Mean healing time was 21 days in the phenytoin group compared to 45 days in the control group ($p<0.05$%).

Topical Phenytoin in diabetic foot ulcer, a study conducted in 1991 by Muthukumarswamy MG et- al, showed the mean time of complete healing of diabetic foot ulcers were 21days with Phenytoin dressing and 45 days with sterile occlusive dressing. The difference seen were statistically significant ($P < 0.05$).[4]

Topical Phenytoin in Diabetic ulcer, a double blind control study conducted by Pai MRSM, Shrivastava N, Kotian MS , showed that there was an acceleration of wound healing in the Phenytoin group particularly around 3rd week but overall reduction in size of the ulcer was not statistically significant ($P> 0.05$).[5]

Trophic Leprosy Ulcers

Bansal and Mukul[9]compared the wound healing effects of topical phenytoin with normal saline in 100 patients with 110 ulcers. Fifty patients were assigned to the

topical phenytoin group and 50 to saline group over a 4 week study period. After 4 weeks, the mean reduction in ulcer volume in the phenytoin group was 72.1 % compared to 55.5% in the control group ($p<0.001$).

The other study by Menezes et al[42] involved a total of 30 patients. Fourteen patients were assigned to topical phenytoin with immobilization and 16 patients to immobilization alone. Both groups showed a significant reduction in depth and surface dimensions of the ulcers at the end of a 3 week study period ($p<0.0l$). The decrease in ulcer depth in the phenytoin group was not statistically significant compared to the control group. However, the rate of decrease in surface dimensions was significant ($p<0.05$) in the phenytoin group compared to the controls.

Chronic Skin Ulcers

Pendse et al[8] studied a total of 75 patients with various types of wounds including burn, post cellulitic, traumatic, amputation stump, postoperative and nonspecific etiology. Forty patients were included in the phenytoin group and 35 patients in the saline dressing group. Fifty percent of the phenytoin-treated wounds showed negative cultures by day 7 vs 17% of the saline-treated group. By the end of the 4-week treatment period, 29 of 40 phenytoin-treated ulcers had healed compared to 10 of 35 controls.

Stage II Decubitus Ulcers in the Elderly

A recent study by Rhodes et al[43] evaluated the wound healing effects of topical phenytoin in comparison to collagen (DuoDerm), or triple antibiotic ointment (TAO). Forty-seven nursing home patients were included in the study. Both the phenytoin and standard treatment groups showed progress in wound healing but the phenytoin group healed faster. In the phenytoin group, healthy granulation tissue appeared within 2 to 7 days (compared to 6 to 21 days for the other two groups). The

average time of healing was significantly shorter for the phenytoin group compared to the standard groups ($p<0.005$). The authors of this study concluded that the use of topical phenytoin can accelerate the healing of pressure sores, and more importantly, can prevent stage II ulcers from progressing to stage III or IV.

Topical Phenytoin Preparation Reported side effect

Topical phenytoin used in wound therapy appeared to be well tolerated. Its adverse effects were used in clinical trials. systemic absorption was considered insignificant. Allergic reaction to topical phenytoin is rare. Formation of thin layer of phenytoin powder on the ulcer, initial burning sensation, skin rash are the other side effects of topical phenytoin which are resolved when application stopped[37,38,43]

A single 100mg phenytoin capsule opened and placed in 5ml sterile normal saline to form a suspension. The sterile gauze was soaked in the suspension and placed over the wound. No adverse reaction reported[43.]

A systematic review conducted between 1963 and 2005 concluded that studies investigating the effect of topical phenytoin on wound healing are of moderate methodological quality and these suggest that there may be a positive effect on wound healing.

SIDE EFFECTS:

Common Side Effects

Long-term parentral phenytoin can lead to a coarsening of the facies, enlargement of the lips and thickening of the scalp and face and also can cause hirsutism.

Collagen Vascular Like Side Effects

Can cause drug-induced lupus, collagen vascular disease, systemic sclerosis, scleroderma and Pseudo-Sjogren syndrome.

Vitamin, minerals and phenytoin

Can alter vitamin levels especially biotin metabolism. Has a variety of effects on copper zinc and magnesium in the hair and skin.

Generalized cutaneous eruptions

Hypersensitivity syndrome

Phenytoin causes a hypersensitivity syndrome that manifests with fever, rash and lymphadenopathy.

Other eruptions

Characterized by edema, discolouration and pain distal to the site of intravenous administration.

Pseudo lymphoma

Patients receiving phenytoin may develop benign lymphoid hyperplasia, pseudolymphoma, Lymphoid hyperplasia can be localized in the cervical areas. Inguinal lymph node can be enlarged , rarely can lead to malignant lymphoma.

Vascular eruptions

Phenytoin can effect clotting function and result in eruption. Dilantin-induced disseminated intravascular coagulation with purpura fulminans.

Birth defects

Prenatal exposure to phenytoin may result in a spectrum of structural, developmental and behavioral changes known as the fetal hydanton syndrome. Varied malformations caused by hydantoin (phenytoin) intake during pregnancy include digit and nail hypoplasia, growth retardation, typical facial appearance, rib anomalies, abnormal palmar creases, hirsutism, and low hairlines. Ambiguous genitalia are rarely associated with this syndrome. A patient with the dysmorphic characteristics of FHS has manifested with unusual hyperpigmentation of several fingernails.

MATERIALS AND METHODS

This prospective randomized comparative study included 60 patients with diabetic ulcers admitted In K.L.E.S. DR. PRABHAKAR KORE HOSPITAL ATTACHED TO J.N.M.C.BELGAUM, from Jan 2010 to Dec 2010 satisfying all the inclusion criteria mentioned below after obtaining consent and clearance from the ethical committee

The inclusion criteria are

- Patients with age between 35 - 70 years
- Patients with blood glucose level between 110 and 130 gm/dl
- Patients with grade one and grade two of wagener's classification.

The exclusion criteria for the study are

- Patients with grade 3, grade 4 and grade 5 ulcers of Wagener's classification.
- Patient with absent peripheral pulses – dorsalis pedis, anterior tibial, posterior tibial artery.
- Patient who is not on regular fallow up and
- not willing to enrol in the study
- Other co-morbid condition like renal failure, generalized debility and other factors, which adversely affect wound healing.

The data was collected from 60 patients who are having diabetic ulcers satisfying all the inclusion criteria mentioned above. The whole sample population was divided into group A and group B based on computerized random number. Group – A contain 30 patients and Group – B contain 30 patients.

All patients underwent detailed clinical examination and relevant

investigations and the wounds were thoroughly debrided and the ulcer dimensions as well as the surface area assessed using measuring tape, before both types of dressings were applied. The control group and study group were subjected to daily dressing. Discharge is sent for culture and sensitivity. Empherical antibiotics are started with ciprofloxacin and metronidazole changed to sensitive antibiotics after sensitivity report. The patients were followed up for 4 weeks in both study and control groups.

Application of Dress:

Group A is dressed with topical phenytoin (study group) and group B with normal saline (control group)

Topical Phenytoin

Phenytoin sodium tablet was crushed and dissolved in 5ml of normal saline to form a suspension. Sterile gauze was soaked in the suspension and spread evenly over the ulcer and left for 24 hours till the next dressing.

Dosage of phenytoin depend on the surface area of ulcer

- 0 to 5 cm^2- 100mg
- 5.1 to 9cm^2- 150mg
- 9.1 to 15cm^2- 200mg
- >15cm^2-300mg.

Control group Dressing was done with normal saline once a day.

Before applying both dressing daily wound is cleaned with normal saline and debridement is done if necessary. Ulcer size is measured initially and at the end of every week for 4 weeks and size is recorded. Size is measured twice and mean of two is taken. Wound is also observed for granulation tissue, discharge at the end of each week and recorded, wound discharge is sent for culture and sensitivity on 10^{th} day of treatment.

Statistical analysis

Unpaired 't' test is used to compare the Mean reduction in size of the ulcer and level of significance chosen at $p<0.05$

Investigations done are:-

- Complete blood count
- Blood urea and serum Creatinine
- FBS
- Serum protein
- X-ray foot AP and lateral view

Ethical clearance is obtained from 'JNMC-Institutional ethics committee on human subject.

RESULTS

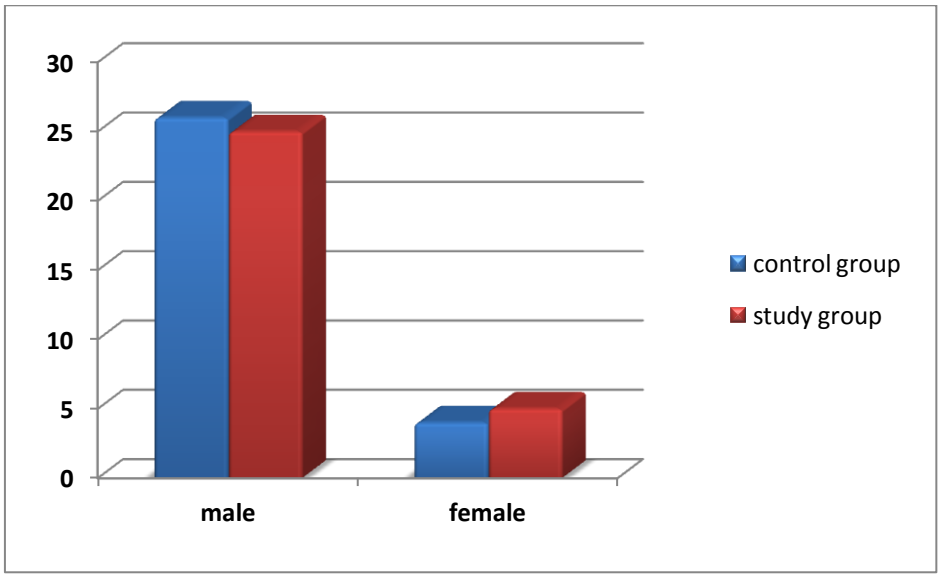
The present study was conducted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum and the findings are tabulated as below.

During the study year from January 2010 to December 2010, 60 patients with Diabetic foot ulcers of the were randomized into study (topical phenytoin dressings) and control (normal saline) group. These groups were studied for the effect of conventional normal saline dressings versus topical phenytoin dressings on wound reduction.

A total of 60 patients satisfied the selection criteria were involved in the study, analysis was done by using unpaired‘t’ test and chi square test.

Table 1: Sex distribution

Groups	Interventional Group		Control group	
	Number	Percentage	Number	Percentage
Males	25	83.3%	26	86.7%
Females	5	16.7%	4	13.3%
Total	30	100.00%	30	100.00%

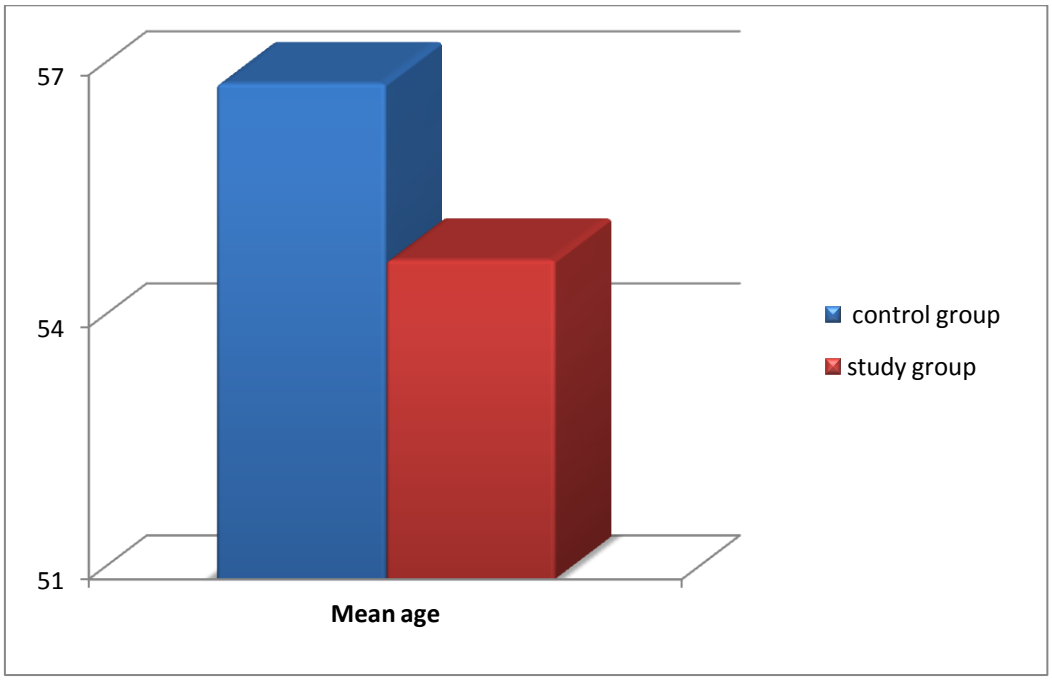


DF=1 P=1

In the interventional group, total number of males and females were 25 (83.33%) and 5 (16.66%) respectively. The male: female ratio was 5:1. In control group, total number of male and females were 26 (86.66%) and 4 (13.33%) respectively. The male: female ratio was 6.5:1. Statistically in this study, there was no significant difference in sex distribution between interventional and control group.

Table 2: Mean age of the patients

Groups	Mean age (Years)	
	Mean	**S.D.**
Cases	54.8	±9.96
Controls	56.9	±10.77
t=0 .784	DF = 58	p= 0.436

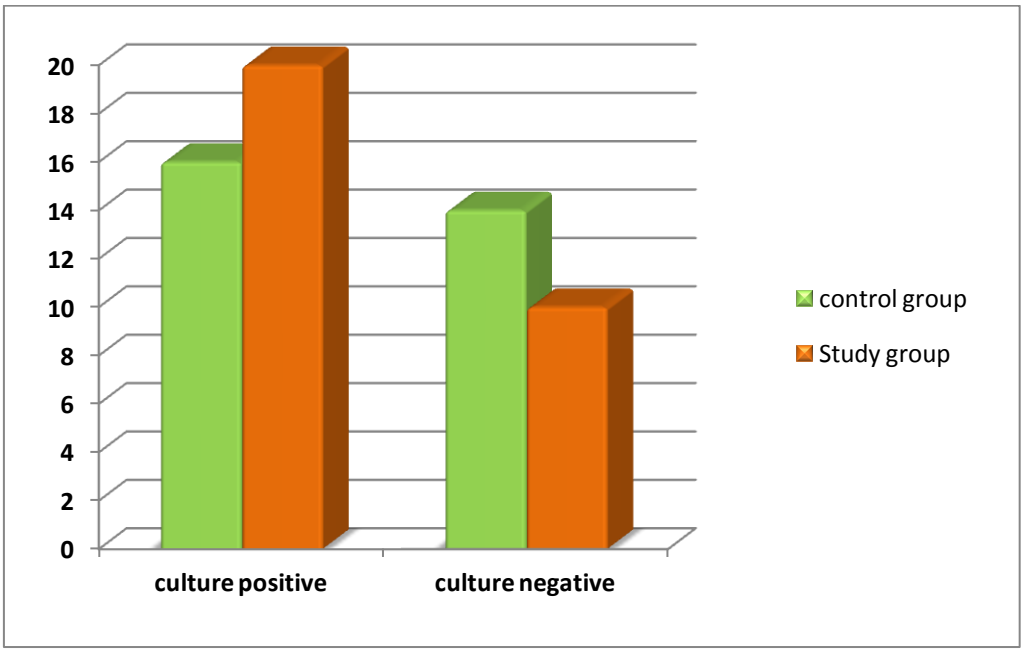


In this study, the mean age in interventional group and control group were 54.8±9.96 and 56.9±10.77 respectively. Statistically there was no significant difference in mean age between interventional and control groups.

Table 3: Culture growth on day 0

Groups	Culture on day 0		
	+ve	_ve	Total
Cases	20(66.7%)	10(33.3%)	30
Controls	16(53.3%)	14(46.7%)	30

X^2=1.111 p=0.292

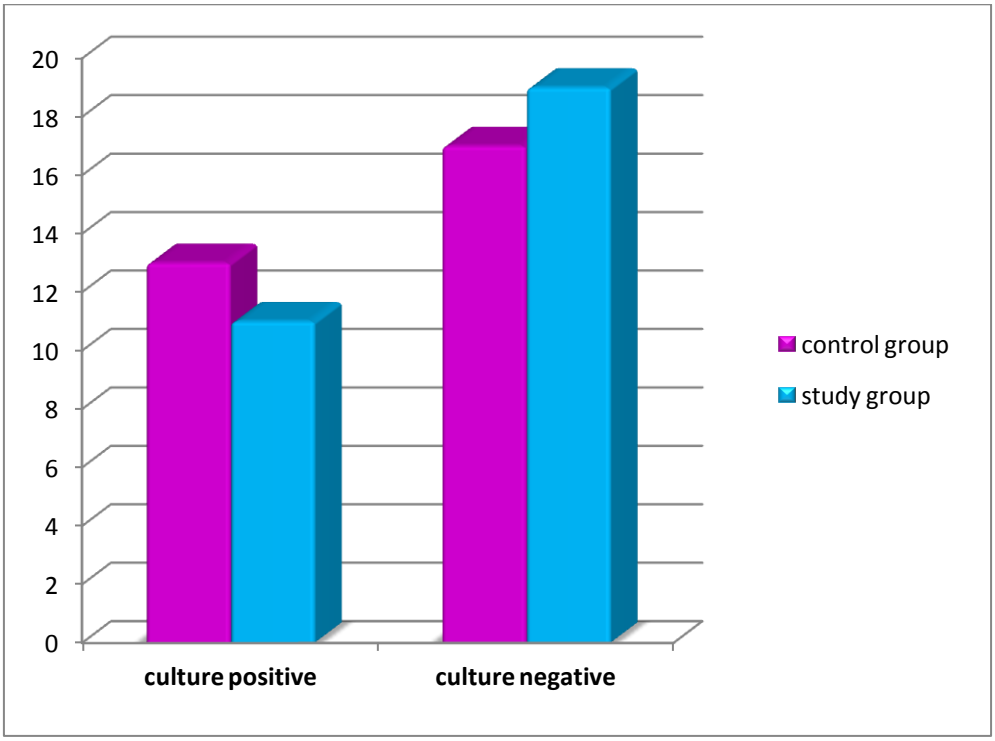


In our study on day zero, 20(66.7%) of 30 patients in study group showed growth on culture and 10 patients showed no organism growth. In control group 16 0f 30 patients showed growth on culture media and remaining 14 showed no growth. There was no significant difference between two groups in positive culture growth on day zero (p=0.292)

Table 4: Culture growth on day 10

Groups	Culture on day 0		
	+ve	_ve	Total
Cases	11(36.7%)	19(63.3%)	30
Controls	13(43.3%)	17(56.7%)	30

X^2= 0.278 p=0.598

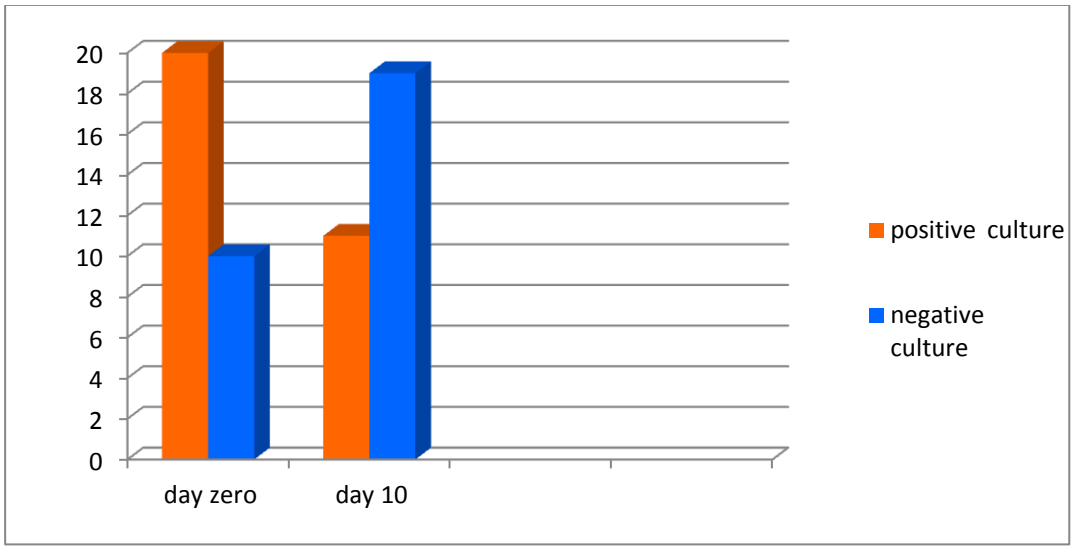


On day 10 of the study 11(36.7%) of 30 patients showed positive for culture in study group and 13(43.3%) of 30 patients were positive for culture in control group. There was no significant difference between two groups for positive culture on day 10 (p=0.598)

Table 5: Culture conversion in study group on day 10

Basal culture	Culture on day 10 in study group		
	+ve	_ve	Total
+ve	11	9	20
_ve	0	10	10
Total	**11**	**19**	**30**

Mc Nemar test **p=0.004**

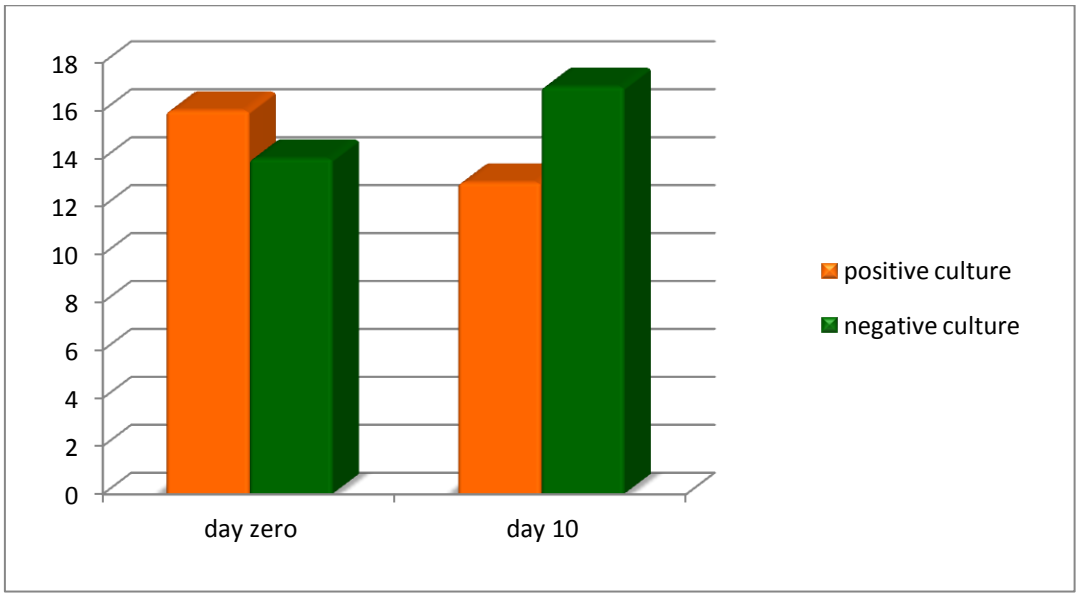


In this study out of 20 patients in study group who were positive for the culture growth on day zero, 9 had no growth on culture on day 10.The Conversion of positive culture on day zero to negative culture on day 10 is statistically significant (p=0.004) in study group.

Table 6: Culture conversion in control group on day 10

Basal culture	Culture on day 10 in control group		
	+ve	_ve	total
+ve	13	3	16
_ve	0	14	14
Total	**13**	**17**	**30**

Mc Nemar test **p=0.250**

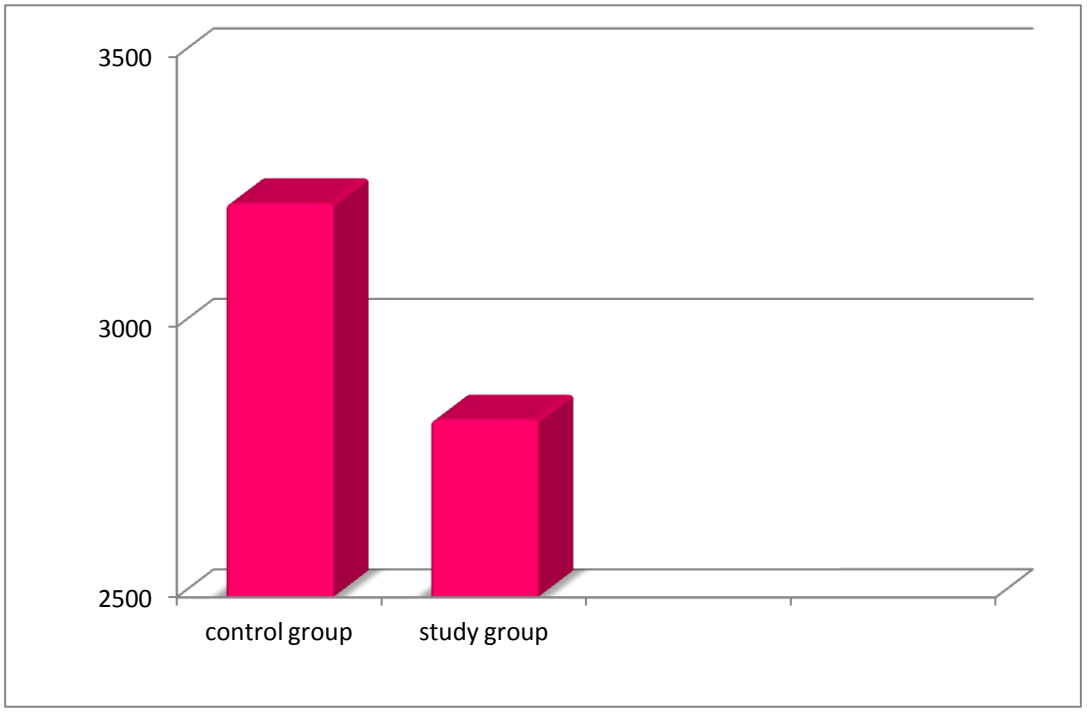


In the control group out of 16 patients who were positive for culture on day zero, 3 had no growth on culture media on day ten. The conversion from positive culture to negative culture on day 10 in control group was not statistically significant (p=0.250).

Table 7: Initial wound area

Groups	Initial wound area (mm^2)	
	Mean	**S.D.**
Study group	2827.1	±1149.1
Controls	3227.8	±1791.8

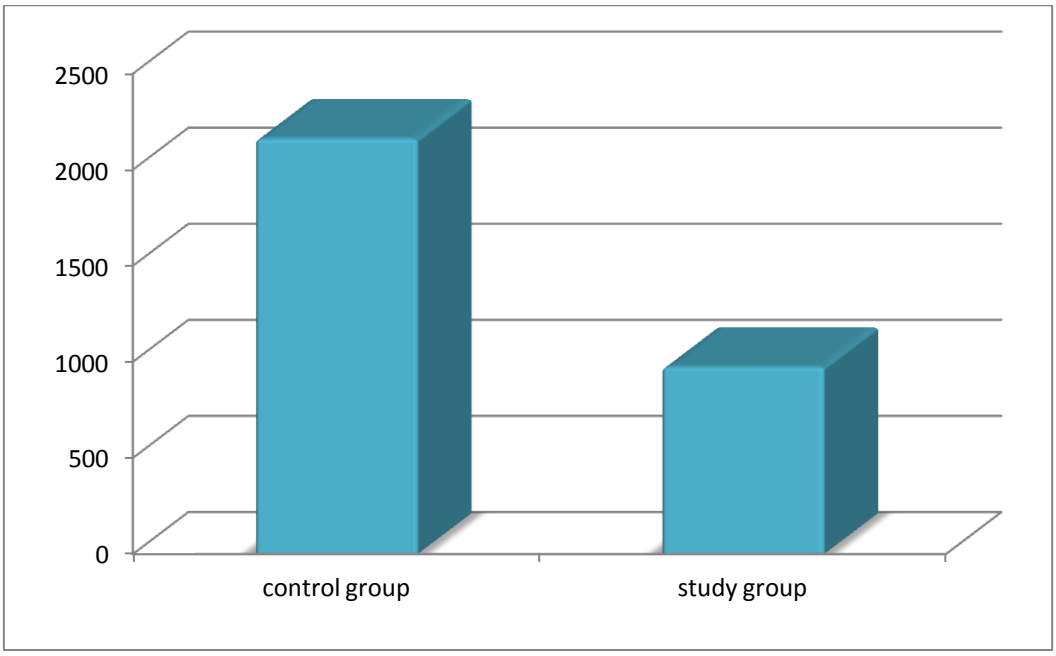
t= 1.03 DF=58 p=0.307



The mean area at the beginning of the study was 2827.1±1149.1 mm^2 in intervention group and 3227.8±1791.8 mm^2 in the normal saline group. There was no significant difference in the initial mean area between the two groups (p=0.307).

Table 8: Final wound area

Groups	Final wound area (mm^2)	
	Mean	**S.D.**
Study group	973.2	±453.3
Controls	2161.0	±1293.2
t= 4.748	DF= 58	P=<0.001

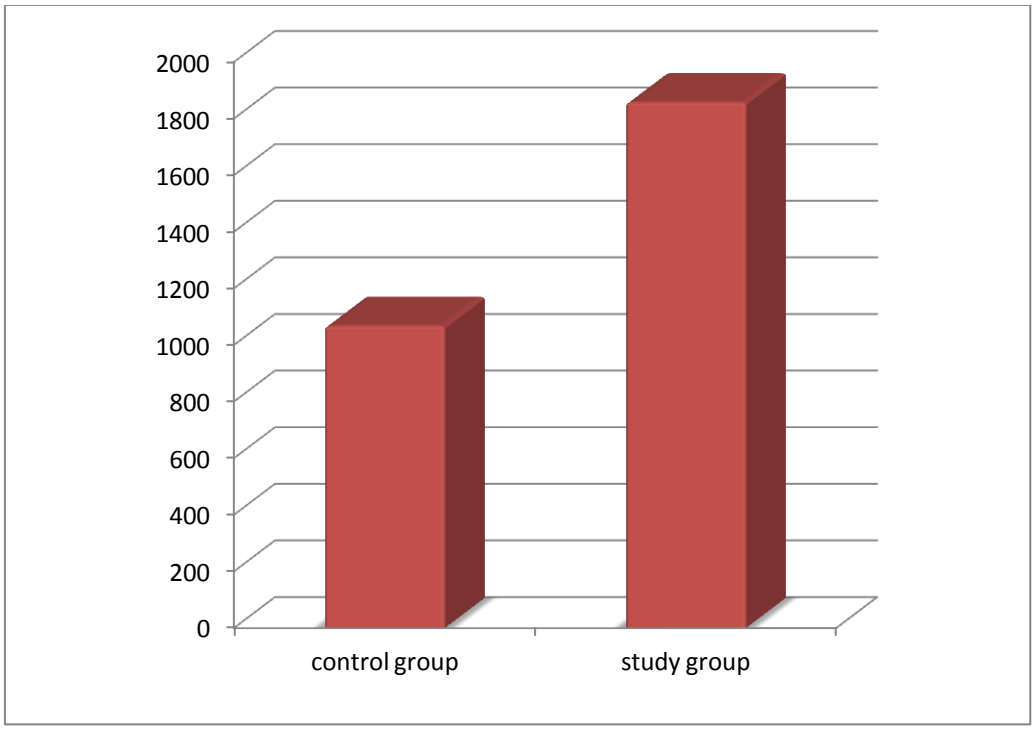


At the end of the study the mean area were 973.2 ±453.3mm^2 in the group treated with topical phenytoin dressings and 2161.0±1293.2mm^2 in the group treated with normal saline dressings. The difference in final wound area between two groups was significant (p=0.001)

Table 9: Wound area reduction

Groups	Reduction wound area (mm^2)	
	Mean	**S.D.**
Study group	1856.9	±724.9
Controls	1066.8	±565.3

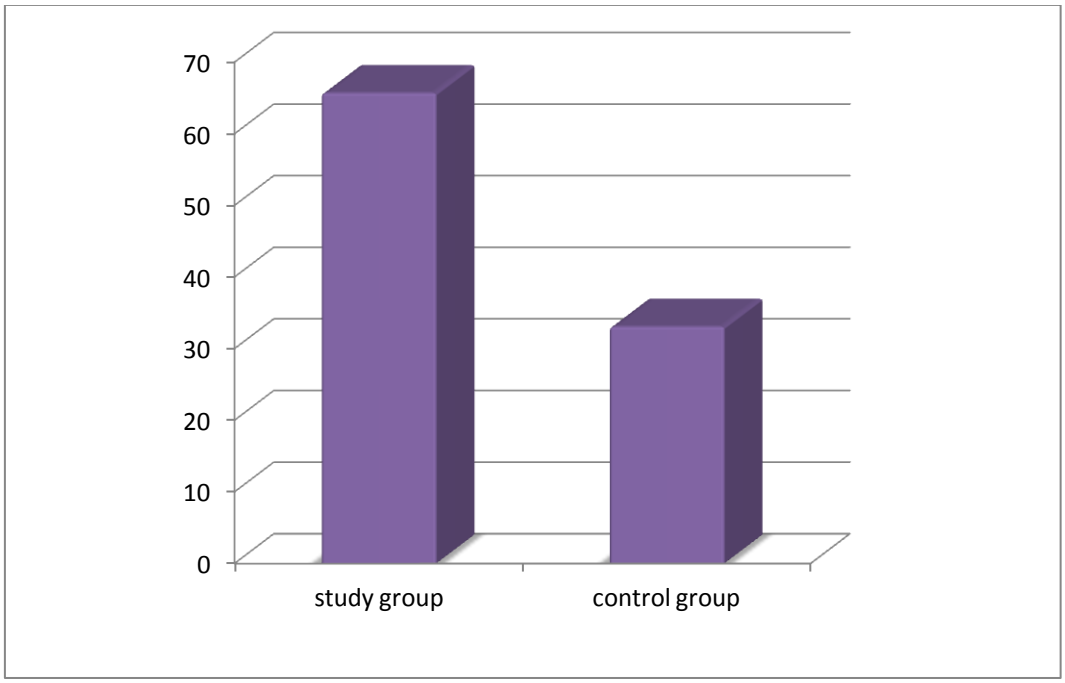
t= 4.707 DF=58 p<0.001



The study shows that the final wound reduction achieved between the two groups were1856.9±724.9mm^2 in patients treated with topical phenytoin dressing and 1066.8±565.3mm^2 in patients treated with normal saline dressing, which is statistically significant (p<0.001).

Table 10: Percentage of reduction in wound area

Groups	Percentage of reduction	
	Mean	**S.D.**
Study group	65.68	±4.6
Controls	33.05	±7.1
t=20.123	DF=58	P=<0.001



The percentage of area reduction were 65.68±4.6 in patients treated with local phenytoin dressing and 33.05±7.1 in patients treated with normal saline dressing, which is statistically significant (p<0.001).

DISCUSSION

It is every surgeon's desire that after dressing the wound, it should heal without any complications. Successful wound dressing should keep the wound moist and be devoid of any adverse reactions such as infection, maceration and allergy. Diabetic foot ulcers are stuck in inflammation phase and shows cessation of epidermal growth or migration over the wound surface.

Phenytoin dressing has shown great promise as a procedure for healing of chronic wounds (Venous ulcers, pressure sores, superficial burn wounds, small donor site wounds and minor abrasions). Phenytoin acts by stimulating fibroblasts enhancing granulation tissue formation, decreasing collagenase activity.[6]

In the present study, an attempt has been made to establish better healing rates with use of phenytoin dressing in diabetic foot ulcer. In this study the base line characteristics such as age, sex and location of the ulcer were similar in the patients who received phenytoin dressing in the study group and in patients who received normal saline dressing in the control group.

This study is a comparative study which is aimed to document the safety and performance of phenytoin dressing in the treatment of established diabetic foot ulcers. Participants had an ulcer size bigger than one cm^2. The treatment period was 4 weeks. The mean wound area reduced from 2827.1mm^2 to 973.2mm^2 in patients dressed with topical phenytoin. Relative wound area reduced from 100% at baseline to 35% at end of 4 weeks in study group. This study demonstrates that treatment of diabetic foot ulcer with topical phenytoin dressing results in considerable wound area reduction and prevents any deterioration in maceration. The percentage of area reduction was 66.2±4.64 in patients treated with topical phenytoin dressing and

33.05±7.1 in patients treated with normal saline dressing.

However, the final area of the ulcer (in mm^2) was significantly reduced in patients with phenytoin dressing group as compared to the patients in normal saline group at the end of the study(p=0.<001). The percentage reduction in the area of the ulcer was more in the phenytoin dressing (66.2±4.64) group as compared to the Normal Saline group (33.05±7.1) and this difference was statistically significant (p=<0.001).

The following formula was applied to calculate % reduction in area of wound after 4 weeks period in both cases and controls.

$$\% \text{ Reduction of wound after 4 weeks} = \frac{\text{Initial area} - \text{Final area}}{\text{Initial area}} \times 100$$

In our study it was noticed that conversion from positive culture to negative culture growth on day 10 was significant in patients dressed with topical phenytoin (p=0.004) and was not significant in patients dressed with normal saline (p=0.250). El Zayat[45] in his study reported reduction of wound contamination with topical phenytoin and postulated it is not a direct anti bacterial effect, but rather a change in the pH and improvement in local circulation;However Lodha[40] et al suggested that phenytoin may have a direct antibacterial effect. Further in vivo and in vitro studies are required to establish the anti-infective effect of topical phenytoin dressing and its mechanism of action.

In this study it was noticed that compared to normal saline, topical phenytoin is more effective in inhibiting wound infection. This conclusion was based on the following findings: earlier appearance of granulation tissue , earlier disappearance of wound discharge and post treatment wound cultures were negative in 9 of 20 patients

who were treated with topical phenytoin , but only in 3 of 16 patients wound cultures were negative in control group , who received normal saline dressing.

Systemic absorption of phenytoin on topical use in diabetic ulcer is not significant. Most studies that have monitored serum phenytoin levels during topical application have shown the levels to be undetectable[44]. Other known side effects of use of topical phenytoin in diabetic ulcer are transient burning sensation initially and Hypergranulation. There were no side effects noted in the patients dressed with topical phenytoin in our study.

Overall this study shows that phenytoin dressing is safe and effective in treating chronic foot ulcers. This study was conducted only for 4 weeks and complete epithelialization and wound reduction was not awaited for.

Limitations of our study

- Not a blinded study
- Follow up is short to derive conclusion on long term healing of the ulcers.

Scope for further study

There is further scope of study among infective diabetic wound with respect to anti-infective properties of topical phenytoin dressing.

CONCLUSION

With the use of topical phenytoin dressing in comparison with the normal saline dressing for the treatment of diabetic foot ulcers , the following conclusions were derived;

- Topical phenytoin dressing showed faster and better healing rates among the study group.
- Area reduction and percentage reduction was better in topical phenytoin dressing group.
- There was no adverse effect or reactions seen when topical phenytoin dressing was applied over the ulcer.
- Appearance of granulation tissue was earlier as compared to regular dressing
- Topical phenytoin dressing may have anti infective effect.

SUMMARY

The present study was conducted in KLES' DR Prabhakar Kore Hospital and Medical Research Centre, Belgaum on 60 patients with diabetic foot ulcers..

The objective of the study was to assess the effect of topical phenytoin dressings with normal saline dressing in healing of diabetic foot ulcers in terms of mean decrease in size of the ulcer.

The two groups were randomized into study (topical phenytoin) and control (normal saline) group. One group received treatment in the form of topical phenytoin dressing and other received conventional normal saline dressing.

There was no statistical difference in the baseline characteristics like age, sex and initial wound area of the ulcer between the two groups.

The final area reduced and percentage of area reduced were statistically significant in the study as compared to the control group.

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ANNEXURE – I

INFORMED CONSENT

TITLE OF THE STUDY: "COMPARATIVE STUDY OF EFFECT OF TOPICAL PHENYTOIN WITH NORMAL SALINE DRESSING IN HEALING OF DIABETIC FOOT ULCERS – A RANDOMIZED CONTROLLED STUDY."

PRINCIPAL INVESTIGATOR: Dr. _____

PROCEDURE:

If you consent to be in this study the relevant data is collected as per proforma and you will be placed in either study or control group.

Initially wound is assessed and if required debridement is done. In study group wound is dressed with phenytoin and in control group dressed with normal saline daily. Wound size assessed at the end of every week for four weeks. Wound exudate is sent for culture on 10th day of treatment.

Wound is observed for granulation tissue quality, discharge and control of infection at the end of each week and noted.

BENEFITS:

- Early wound healing

RISKS:

- Burning sensation at the start of treatment
- Hypergranulation
- Hypersensitivity

ALTERNATIVES:

1. VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is voluntary. I may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. My decision will not change the present or future health care or other services that I receive. The study doctor or the sponsor may stop my participation in this study. I will tell of any important new findings that may change my willingness to continue to take part. If I choose not to take part in the study I will receive the standard treatment for patients with my condition.

COSTS:

Cost of phenytoin capsules is around Rs. 200/- to 300/-

COMPENSATION:

As the subject voluntarily consents to be a part of the study, no compensation will be given.

CONFIDENTIALITY:

All information collected about me during the course of the study will be kept confidential to the extent permitted by the law. The code numbers will identify me in this research record. Information from this study may be published but my identity will be confidential in any publication.

QUESTION:

If any enquiries in the future or in case of research related injury illness, you may contact following person.

Dr. _____

J.N. Medical College,
Belgaum
Ph.No. 0831-2473777
Ext. 1740

Dr. _____

J.N. Medical College,
Belgaum
Ph.No. 0831-2473777
Ext. 1740

CONSENT FORM

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

Signature /Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ : …….

Signature/ Left Thumb
Impression of the participant's : …….

Name of the legally
authorized representative/ Guardian : …….

Signature/ Left Thumb
Impression. : …….

Witness's Name : …….

Signature/ Left Thumb
Impression. :…….

Investigators name and Signature : …….

Date and Place : …….

ANNEXURE - II

PROFORMA

I. PATIENT IDENFICIATION DATA

GROUP : CASE NO. :

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

NAME : D.O.S:

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 : ( )

Complication:

Neuropathy : ( )

Vasculopathy : ( )

V. ULCER DETAIL

1. Mode of onset

Traumatic : ( )

Spontaneous : ( )

Pressure : ( )

Others : ( )

2. Duration

3. Progress

VI. WOUND OBSERVATION

1. Site
2. Size
3. Shape
4. Edge
5. Margin
6. Floor
7. Base
8. Discharge
9. Surrounding Skin
10. Contraction

VII. NEUROLOGICAL EXAMINATION

VIII. VASCULAR EXAMINATION Right

Left

Popliteal a.

Ant. Tibial

Post Tibial

Dorsalis Pedis

IX. ANY FOOT DEFORMITY PRESENT

Toe deformity

Bunion

Charcots foot

Foot drop

X. IF AMPUTATION HAS BEEN DONE

Specify, Date :

Side :

Level :

Cause for amputation:

XI. INVESTIGATION

CBC

FBS Date Time

Blood Urea

Sr. Creatinine

Urine :

Routine

Microscopy

X-ray Foot

AP view

Lat. View

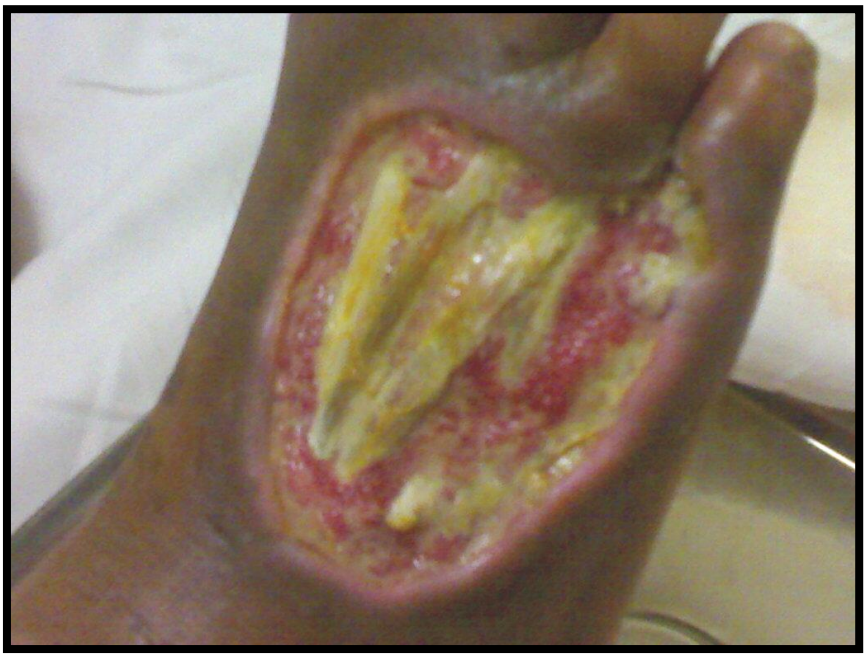
Tissue culture/ sensitivity

Before dressing

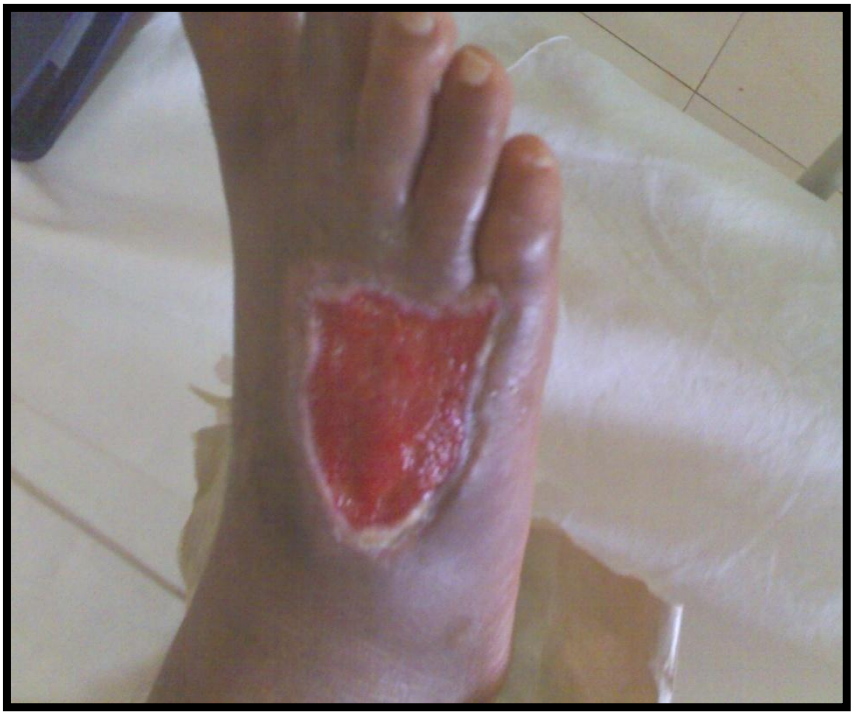
10 days after dressing.

ANNEXURE III

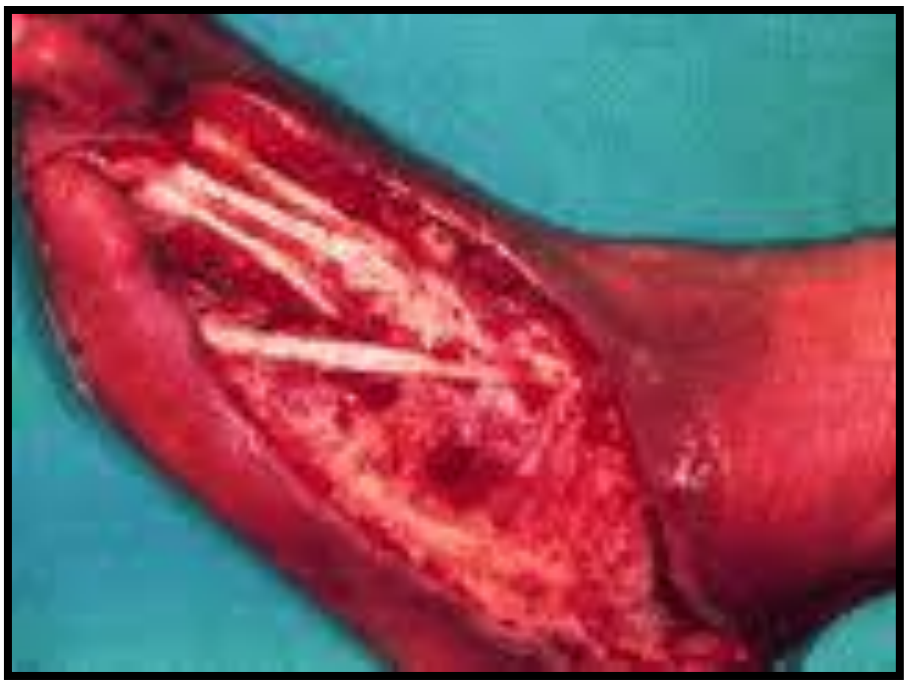
PHOTOGRAPHS



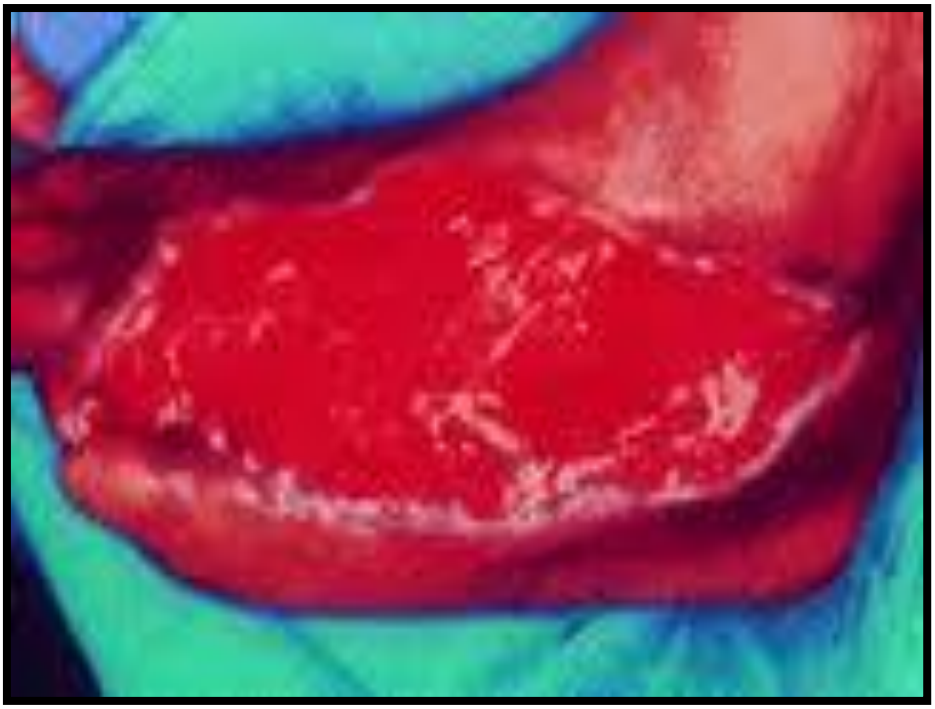
Photographs 1: Ulcer size on day one



Photographs 2: Ulcer size after 4 weeks using Phenytoin dressing



Photographs 3: Ulcer on day one



Photographs 4: Ulcer after 2 weeks using Phenytoin dressing

KEY TO MASTER CHART

DRF : Dorsum of right foot

DLF : Dorsum of left foot

DM : Diabetes mellitus

I : Insulin

O : Oral hypoglycemic

FBS : Fasting blood sugar

N : Normal foot X-ray

mm : mille meter

_ : No growth on culture

\+ : Growth on culture present

ANNEXURE – IV -MASTER CHART OF CONTROL GROUP

S. No	I.P No	GROUP	AGE /sex	Site	Anti DM Rx	x- ray	culture	Culture at 10^{th} day	Initial area in mm^2	Final area in mm^2	Reduction in area mm^2	% of area reduction
1	333884	Control	63/M	DLF	O	N	_	_	6075	3538	2537	41.7
2	340320	Control	55/M	DRF	O	N	+	+	4740	3117	1623	34.2
3	337766	Control	63/M	DRF	I	N	+	+	1952	1361	591	30.2
4	340421	Control	68/M	DRF	I	N	+	+	6000	4668	1332	22.2
5	369693	Control	65/M	DRF	O	N	+	_	6000	3950	3300	34.1
6	371057	Control	61/M	DRF	I	N	_	_	2385	1633	752	31.5
7	372061	Control	61/M	DLF	I	N	_	_	3150	2100	1050	33.3
8	372331	Control	58/M	DRF	O	N	_	_	1824	1295	529	29.0
9	373766	Control	60/M	DLF	I	N	_	_	2275	1314	961	42.2
10	336604	Control	70/M	DLF	O	N	+	+	7950	5681	2269	28.5
11	377792	Control	55/F	DRF	I	N	+	+	3496	2322	1175	33.5
12	333884	Control	60/M	DRF	O	N	_	_	7680	5707	1973	25.7
13	375816	Control	55/M	DLF	O	N	_	_	8600	5220	3380	39.3
14	376624	Control	65/M	DLF	I	N	+	+	7504	5581	1923	25.6
15	377571	Control	39/M	DLF	I	N	+	+	3120	2153	967	30.9
16	378616	Control	36/M	DLF	I	N	_	_	5022	3053	1969	39.2
17	353038	Control	43/M	DLF	O	N	_	_	2077	1521	556	26.7
18	380165	Control	39/M	DRF	O	N	+	+	836	477	359	42.9
19	382375	Control	52/M	DLF	O	N	_	_	1200	676	524	43.6
20	387534	Control	36/M	DRF	I	N	_	_	5418	3386	2032	37.5
21	385033	Control	68/M	DRF	O	N	+	_	1449	838	611	42.6
22	385909	Control	58/M	DRF	O	N	+	+	4964	3426	1538	30.9
23	386245	Control	52/M	DLF	O	N	+	+	4284	3029	1255	29.2
24	386589	Control	61/F	DLF	O	N	+	+	782	382	400	51.0
25	387616	Control	65/F	DRF	O	N	+	+	1860	970	890	47.8
26	389789	Control	60/M	DLF	O	N	_	_	2232	1610	622	27.8
27	389988	Control	36/M	DLF	O	N	+	+	1050	644	406	38.6
28	390854	Control	69/M	DRF	O	N	_	_	2835	1857	978	34.4
29	341341	Control	68/M	DLF	I	N	+	_	2070	1553	517	24.9
30	395842	Control	68/F	DLF	I	N	_	_	6600	4029	2571	38.9

MASTER CHART OF STUDY GROUP

S. No	I.P .No	GROUP	Age/Sex	Site	Anti DM Rx	X-ray	Culture	Culture at 10^{th} day	Initial area in mm^2	Final area in mm^2	Reduction in area mm^2	% of area reduction
1	330340	Case	55/F	DRF	O	N	+	+	4030	1500	2530	62.9
2	338550	Case	54/M	DRF	O	N	+	_	1800	580	1220	67.7
3	348208	Case	42/M	DRF	O	N	+	_	4536	1794	2742	60.4
4	350072	Case	65/F	DLF	I	N	+	+	4880	1489	3391	69.4
5	360252	Case	70/M	DRF	I	N	_	_	2460	701	1759	71.5
6	368708	Case	62/M	DLF	I	N	+	_	1938	617	1321	68.1
7	371640	Case	51/M	DLF	O	N	+	+	972	219	753	77.4
8	372040	Case	72/M	DRF	O	N	+	+	2464	715	1749	70.9
9	372996	Case	58/M	DRF	I	N	+	_	1920	649	1271	66.0
10	347460	Case	55/M	DLF	O	N	_	_	1800	477	1323	73.5
11	375534	Case	60/M	DRF	O	N	_	_	1760	675	1085	61.6
12	338765	Case	49/M	DLF	O	N	_	_	3358	974	2384	70.9
13	326155	Case	41/M	DRF	O	N	+	_	2100	727	1373	65.3
14	375599	Case	42/M	DRF	I	N	+	+	1800	584	1261	67.5
15	377472	Case	35/M	DRF	I	N	_	_	3648	1360	2278	62.4
16	377729	Case	47/M	DLF	I	N	+	_	3150	1152	1998	63.4
17	378749	Case	37/M	DRF	I	N	_	_	3120	1302	1818	58.2
18	342536	Case	57/M	DRF	O	N	+	+	2205	681	1524	69.1
19	345052	Case	63/F	DLF	I	N	_	_	2112	679	1433	67.8
20	384158	Case	67/M	DRF	O	N	_	_	2880	836	2044	70.9
21	384578	Case	65/M	DLF	O	N	+	+	2508	999	1509	60.1
22	386045	Case	58/M	DRF	I	N	+	+	3150	1158	1992	63.2
23	386824	Case	45/M	DLF	O	N	+	_	5843	2210	3683	62.4
24	377792	Case	55/F	DRF	O	N	_	_	4880	1678	3202	65.6
25	386916	Case	42/F	DRF	O	N	+	+	2537	799	1738	68.5
26	389613	Case	55/M	DLF	O	N	+	_	2494	1007	1487	59.4
27	389502	Case	55/M	DLF	O	N	+	+	1794	571	1223	68.1
28	391024	Case	59/M	DLF	O	N	_	_	3472	1389	2083	59.9
29	391608	Case	65/M	DLF	I	N	+	_	3654	1115	2539	69.4
30	394179	Case	65/M	DLF	O	N	+	+	1548	558	990	63.9