

The Role of Topical Phenytoin In The Management Of Diabetic Foot Ulcers

Elamaran. E¹, Sathish. V. T²

¹Assistant Professor, Department Of General Surgery, Govt. Rajaji Hospital, Madurai, India

²Assistant Professor, Department Of General Surgery, Govt. Rajaji Hospital, Madurai, India

*Corresponding Author: Elamaran. E

ABSTRACT : Diabetes is a global epidemic with devastating human, social and economic consequences. The disease claims as many lives per year as HIV/AIDS and places a severe burden on healthcare systems. Diabetic foot problems are among the most serious and costly complications of diabetes. The rising prevalence of diabetes all over the world has brought with it an increase in the number of lower limb amputations performed as a result of the disease. A majority of these amputations are preceded by ulcers. Both ulcers and amputations have an enormous impact on people's lives, often leading to reduced independence, social isolation and psychological stress. The diabetic foot is also a significant economic problem, particularly if amputation results in prolonged hospitalization, rehabilitation, and an increased need for home care and social services. By implementing a care strategy that combines prevention, the multidisciplinary treatment of foot ulcers, appropriate organization, close monitoring, and education of people with diabetes and healthcare professionals, it is possible to reduce amputation rates by up to 85%. This study was undertaken to study the various factors influencing the DFU healing and to study the effect of topical phenytoin in the management of Diabetic Foot Ulcers (DFU).

Keywords – amputation, diabetes, foot, phenytoin, ulcer,

I. INTRODUCTION

The World Health Organization defines the diabetic foot as “**an infection, Ulceration and / or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb**”.

The foot is especially affected by diabetes because:

- Diabetes damages the nerves -damage can occur to the foot and not be detected.
- Diabetes also affects the circulation which can affect the ability of the body to heal when damage occurs.
- Those with diabetes are more prone to infection.
- Diabetes can also affect the joints, making them stiffer.

Other diabetes complications that can also affect the foot, for example, kidney disease (affects proteins that are involved in wound healing) and eye disease (can't see the foot to check for damage). The principal pathogenic mechanisms involved in diabetic foot disease include,

1. Neuropathy
2. Ischemia
3. Infection

Diffuse Peripheral neuropathy is further classified into[1,2,3]

1. Sensory Neuropathy
2. Motor Neuropathy
3. Autonomic Neuropathy

Oral phenytoin is used widely for the treatment of convulsive disorders and about half the patients treated develop gingival overgrowth as a side effect. The apparent stimulatory effect has prompted its assessment in wound healing. The mechanism of action has been postulated to be multifactorial. Phenytoin accelerates wound healing and improves the quality and vascularity of granulation tissue by

- Increasing fibroblast proliferation
- Increasing collagen content and maturation.
- Decreasing collagenase activity.

Shafer investigated the stimulatory effect of phenytoin sodium on cell lines from normal and neoplastic tissues. Phenytoin increased proliferation 50-90 percent in two fibroblast cell lines, but had no effect on cells derived from heart, kidney, lung, intestine, squamous epithelium, or four of five tumor cell lines.

Vijayasingham et al. found no stimulation of proliferation of human dermal fibroblasts or epidermal keratinocytes in culture. They proposed that phenytoin may act indirectly *in vivo* on keratinocytes by affecting membrane transport of cations, which in turn alters cytokine and growth-factor activities that affect inflammatory cells. Alternatively, it is possible that only certain subgroups of functionally-distinct fibroblasts respond to phenytoin.

In a guinea pig model of wound healing, it was found that phenytoin more readily cleared gram negative organisms than gram positive bacteria from wounds. Local pain relief has also been observed with topical phenytoin therapy, which can be explained by its membrane-stabilizing action; the reduced inflammatory response may also contribute. Facilitation of nerve regeneration has also been reported with phenytoin. In 1939 Kimball first observed that **gingival hyperplasia** occurred in some patients treated with phenytoin; this stimulated the study regarding the potential use of phenytoin in wound healing. Shapiro carried out the first controlled clinical trial in 1958, finding that periodontal patients with surgical wounds who were pretreated with oral phenytoin had less inflammation, less pain, and accelerated healing compared with controls. Subsequently, phenytoin was found to promote the healing of dental extraction sockets and to increase the tensile strength of experimental skin and corneal wounds. Accelerated fracture and periosteal healing with systematically administered phenytoin was observed in several animal studies. The earliest clinical study of phenytoin in cutaneous wound healing used oral phenytoin sodium to treat **venous stasis ulcers** in 28 patients in a double-blind, placebo-controlled trial. At the end of 13 weeks, the mean-wound area in the treatment group decreased by 0.65 cm², whereas in the control group, the lesion area increased by 7.7 cm². Bansal and Mukul compared topical phenytoin with sodium chloride (0.9 %) dressing in the treatment of **leprosy trophic ulcers**. Comparable efficacy has been shown by Malhotra and Amin, Menezes et al. and Bogert et al. in **trophic leprosy ulcers**. El Zayat examined the effects of topical phenytoin in comparison with chlorhexidine and hydrogen peroxide in fifteen patients with intractable **decubitus ulcers and missile wounds**. Phenytoin was used in the treatment of **gluteal abscesses** secondary to intramuscular injection by Lodha et al. Pendse et al. compared phenytoin with sodium chloride (0.9 %) dressings in 75 patients with **chronic wounds of various etiologies** (burns, cellulitis, trauma, amputation stump, postoperative). Oluwatosin et al. compared topical phenytoin with honey dressings for the treatment of chronic leg ulcers and found that phenytoin was superior to honey as a topical agent. Second- and third-degree **burn wounds** were also treated with phenytoin and compared to silver sulfadiazine cream. Phenytoin may also be useful in enhancing the healing of **clean surgical wounds**. Phenytoin has also been tried in healing of **decubitus ulcers**. Favorable therapeutic responses have been reported in open trials with oral phenytoin in patients with **epidermolysis bullosa**. [4,5,6,7]

Modaghegh et al. compared four topical phenytoin formulations (gel, cream, phenytoin sodium powder, and phenytoin powder) in a rat model of wound healing and concluded that the phenytoin powder showed the most favorable results. Some patients have a transient burning sensation when the powder is initially applied, but this can be prevented by using pure phenytoin powder instead of phenytoin sodium. A generalized rash that resolved when treatment was stopped has also been reported. Hypertrophic granulation tissue was noted in 10-36 percent of patients in two studies. This is reversed by stopping treatment, and it is suggested that stopping treatment when the wound area is covered with a granulation base can prevent this effect. Systemic absorption of topical phenytoin is not significant. Most studies that have monitored serum phenytoin levels during topical application have shown the levels to be undetectable.

P.M.R. Carneiro and E.T.M. Nyawawa have compared topical phenytoin versus EUSOL in the treatment of chronic leg ulcers and has found that phenytoin powder is cheap and easily applied topically on ulcers effectively relieves pain, clears discharge and enhances formation of granulation tissue thereby promoting healing. MRS M. Pai, N. Sriram, M.S. Kotan had found in their randomised control studies that topical phenytoin decreases the ulcer area, quality of granulation, decrease in wound discharge, and decreased infection. Muthuumarasamy MG, Sivaumar G, Manoharan G. Topical phenytoin in diabetic wound ulcers. Diabetes care 1991 have also confirmed effectiveness of topical phenytoin in diabetic foot ulcer. [8,9]

II. HEADINGS

1. Introduction

2. Materials and Methods

2.1 Materials

2.2 Methods

2.3 Sample size

2.4 Patient selection

2.5 Proforma

2.6 Investigations

MATERIALS

METHODS

SAMPLE SIZE

PATIENT SELECTION

INCLUSION CRITERIA:

- DFU with ulcer involvement limiting to the foot
- DFU of WAGNER's grade from Gr1(superficial involvement)to Gr4(gangrene limited to forefoot or heel).
- DFU with no vascular compromise

EXCLUSION CRITERIA:

- Patients Moribundly ill.
- Patients with Diabetic Ketoacidosis.
- Patients with erratic blood glucose control
- Patient with poor compliance
- Patients with vascular compromise
- Patients with WAGNER's grade 5 Ulcer(extensive gangrene of foot and leg)

PROFORMA

Name: _____ Age: _____ sex: _____ Residence: _____
Chief complaints of: _____ H/of Ulcer how many wks/months _____
 _____ H/of Pain _____

H/of Present illness:

- Initiating event
- H/of claudication/rest pain
- H/of fever or chills
- H/of abdominal pain /vomiting /giddiness/palpitation/diaphoresis
- H/of tingling or numbness sensation over the legs

H/ of Past illness:

- H/of recurrent healing of ulcers in the foot
- H/of Diabetes for how many years
- H/of treatment for HT/Bronchial Asthma/
- H/of any chronic drug intake/previous surgery

Personal H/o:

-Smoker/Alcoholic/Bare foot walker/H/of trauma

Family H/of:

-Family H/of Diabetes

General Examination:

Built, Nourishment, anaemic status, jaundice, pedal edema,

PR:

BP:

Systemic Examination:

CVS:

RS:

P/A:

CNS:

EXAMINATIONS OF ULCER:

INSPECTION: Site of ulcer
Size and shape
Number, Position
Edge, Floor
Discharge
Surrounding areas

PALPATION: Tenderness
Edge and margin
Base and depth
Relation to deeper structures
Surrounding skin
Gangrene
Callus Foot deformity

GRADING OF THE ULCER BASED ON WAGNERS STAGING:

Vascular examination: Palpation of pulses (DP, PT, Popliteal, femoral)
Venous filling time
Capillary refill
Colour changes
Oedema
Temperature gradient
Skin changes

INVESTIGATIONS:

-Urine albumin/sugar /deposits/acetone
-Blood urea/sugar/creatinine/electrolytes
-Blood grouping and typing
-Lipid profile
-X-Ray of the involved leg
-Wound culture and sensitivity
-ECG
-Doppler study of the legs

RESULTS

- Of the 40 diabetic foot ulcer patients the majority of the patients belong to 60-70 yrs of age and the next common presentation was between 50-60 yrs.(TABLE 1; Fig 1)
- Of the 40 patients 32 patients were male and 8 were female.(Fig 2)
- Of the patients having diabetic foot ulcers majority of them had diabetes for 5-10 yrs.(TABLE 2; Fig 3)
- Of the patients, 12 patients were bare foot walkers and 28 patients were walking with footwear.(TABLE 3; Fig 4)
- Of the 40 patients 10 patients had some form of renal dysfunction as elevated renal parameters or USG showing medico renal disease.(TABLE 4 ; Fig 5)
- Of the 40 patients 26 patients had strict glycaemic control with Insulin and 14 patients had moderate glycaemic control(Blood glucose: 200-300mg) .(TABLE 5; Fig 6)

➤ **WAGNER's GRADING:**

○ Of the 40 patients majority of the patients were of grade 3 and 4 (abscess with osteomyelitis and DFU with forefoot/toe gangrene). Patients presenting with grade 1 and 2 ulcers are relatively rare.(TABLE 6; Fig 7)

➤ **WAGNER's Grading of Ulcer:**

- Grade 1- Superficial ulcer
- Grade 2- Deep ulcer
- Grade 3-Abscess with Osteomyelitis
- Grade 4- Forefoot /Heel Gangrene
- Grade 5- Extensive Gangrene of the foot

➤ Of the 40 patients , 10 patients had ulcer over the plantar surface, 7 patients had ulcer on the dorsum of foot, 4 patients had ulcer over the heel and 19 patients had ulcer over both the plantar and dorsal surface. (TABLE 7; Fig 8)

➤ Most common organism isolated from the wound was Proteus.(TABLE 8; Fig 9)

➤ At the end of 2 weeks of monitoring of topical phenytoin these were the end results.(Fig 10)

➤ Unhealthy wound -14

➤ Healthy granulating tissue-23

➤ Ascending infection-BK amputation-2

➤ Death due to comorbid illness-1

➤ The effects of topical phenytoin on DFU was studied based on the following findings

- -Regression of severity of pain(TABLE 9)
- Nature of discharge(purulent/serous)(TABLE 10)
- -Appearance of healthy granulation tissue.(TABLE 11)

IV. DISCUSSION

The appearance of granulation tissue at the end of 2nd week was comparably earlier and higher in patients treated with topical phenytoin than with controls

AGE INCIDENCE:

The commonest age incidence in the study was between 60-70 yrs which represents nearly 50% of the patients. The next common age of presentation was 50-60yrs which accounted for nearly 30%. Age of presentation < 50yrs and > 70yrs are 10%. The age groups involved in our present study is similar to that reported from Karl Franzens University, Austria(Mean age 66 years) and by Hasbun et al from Mexico Hospital48(Mean age 60+/-4 years). A study was undertaken in the USA in 2004 through the 2002 National Hospital Discharge Survey, looking at 275,000 in patient records from 500 hospitals since 1996. The study revealed that elderly Diabetics had twice the risk of developing a foot ulcer, three times the risk of developing a foot abscess and four times the risk of developing Osteomyelitis.

SEX INCIDENCE:

In this study the incidence in males was about 80% and in the female it was about 20%. This may be probably due to risk factors like manual labour, trauma and smoking in males.

In our study 65% of patients were chappal wearers and they would have developed diabetic foot ulcers due minor trauma or ill fitting chapals or during nail cutting.

DURATION OF DIABETES:

Patients having diabetes for 5-10yrs were the common with a representation upto 50% of patients in this group This implies greater the duration, greater is the risk of developing foot ulcer.

RENAL DYSFUNCTION:

In our study 25% of patients presented with renal dysfunction in the form of elevated renal parameters or USG showing medicorenal disease. In patients with associated renal dysfunction the outcome is inferior comparing with the normal renal function patients

GLYCAEMIC CONTROL:

In our study 65% of patient were having strict glycaemic control with insulin and 35% had moderate control of blood glucose values.

GRADING OF ULCER:

In our study 43% of patients had wagner's grade 3 ulcer(abscess with osteomyelitis). Grade 4 ulcer were representing 30% patients(ulcer with forefoot gangrene). Grade 2 ulcer(deep ulcer) was present in 25% of patients. Grade 3 grade 4 ulcers were the commonest presenting ulcer in Govt Rajaji Hospital. Most of the

patients either presented with deep seated abscess, and forefoot gangrene. Patients presenting with either grade 1 and grade 2 ulcer is rare reflecting the lack of awareness of diabetic foot.

SITE OF DFU:

In our study majority of patients (48%) had ulcers involving plantar and dorsal aspect. 25% patients had ulcers in the plantar aspect only and 17% patients had ulcer in the dorsal aspect only. 10% of patients had ulcer in the heel. Plantar area is the weight bearing area and often gets unnoticed and hence the commonest area of DFU.

WOUND CULTURE:

In wound culture and sensitivity on the initial day the majority of patients showed gram negative organisms (Proteus and E.Coli) and the next common being staphylococci and Pseudomonas.

EFFECTS OF TOPICAL PHENYTOIN:

REGRESSION OF PAIN:

Comparing the control group the topical phenytoin treated groups have greater regression of pain in the end of 2nd week. The pain was quantified based on the need for analgesics. This is a more of a subjective finding.

CLEARANCE OF WOUND DISCHARGE:

At the end of 2nd week significant number of patients in phenytoin treated group has decrease in the pus discharge and had either no discharge or only serous discharge.

WOUND CULTURE

Phenytoin treated patients significantly showed wound negative for culture at the end of 2nd week week than with the controls.

GRANULATION TISSUE:

The appearance of granulation tissue at the end of 2nd week was comparably earlier and higher in patients treated with topical phenytoin than with controls.

V. FIGURES AND TABLES

Table 1 – Age Distribution

AGE	No of persons
40-50 yrs	4
50-60yrs	12
60-70yrs	20
>70 yrs	4

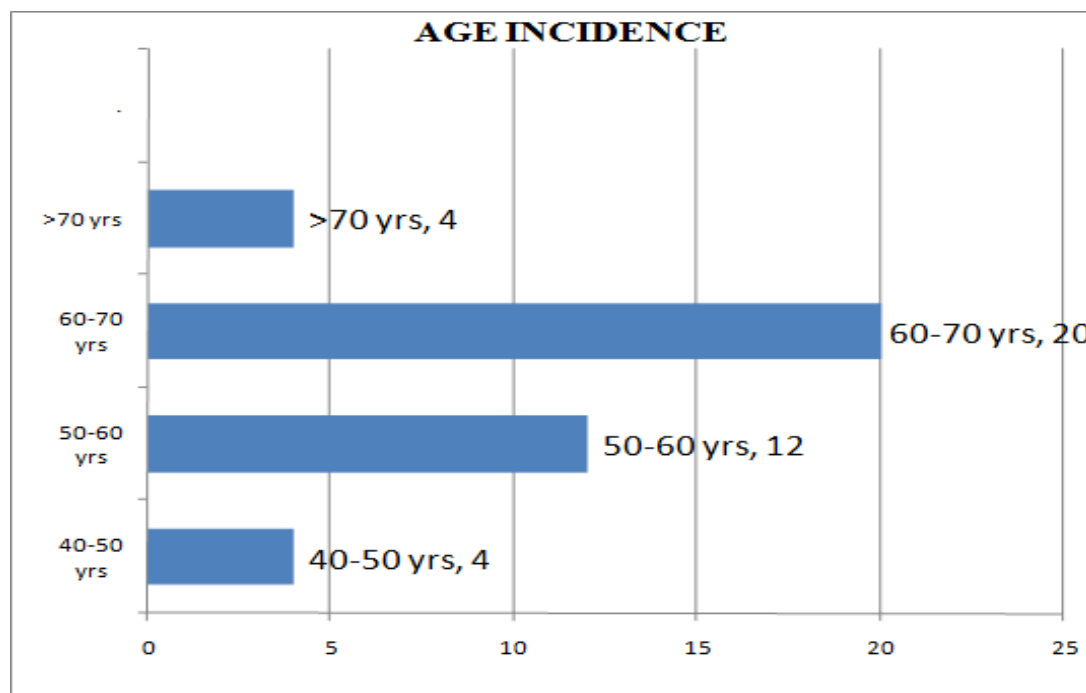


Fig 1 – age distribution

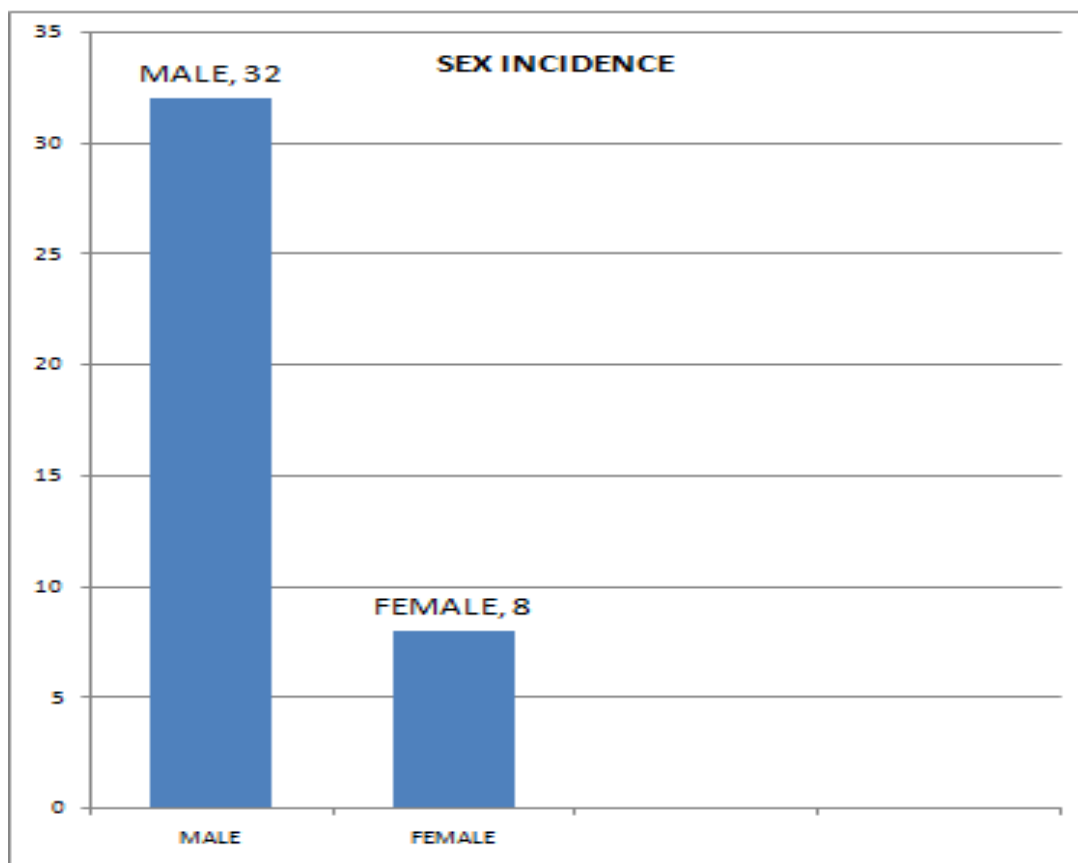


Fig 2 – sex distribution

Table 2 – Duration of Diabetes

Duration of Diabetes	No. of persons.
<5 yrs	15
5-10 yrs	20
>10 yrs	5

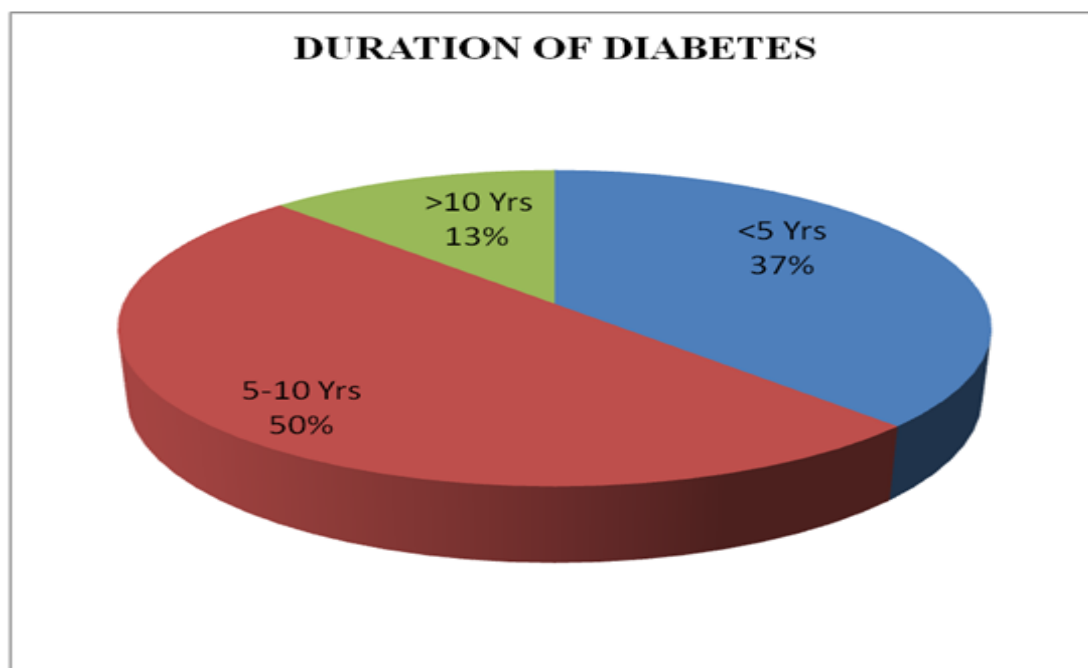


Fig 3 – duration of diabetes

Table 3 – Barefoot and Persons wearing footwear

BARE FOOT WALKERS	12
PERSONS WEARING CHAPPALS	28

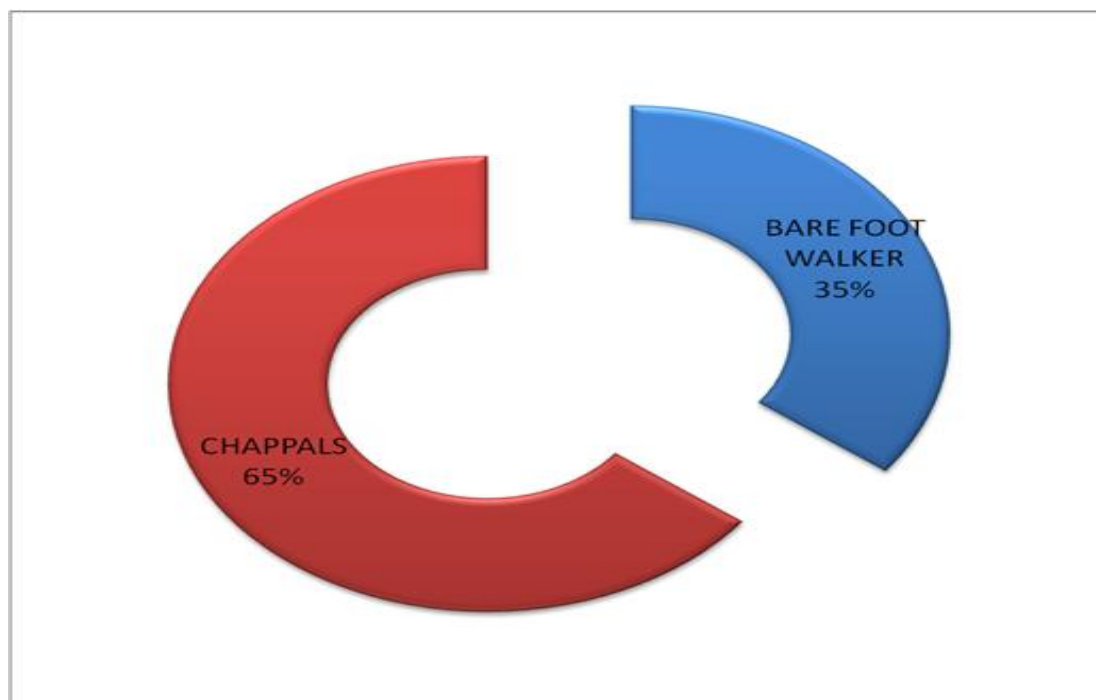


Fig 4 – Barefoot walkers and persons wearing footwear

Table 4 – Distribution of Renal Disease

Associated renal dysfunction	10
With normal renal function	30

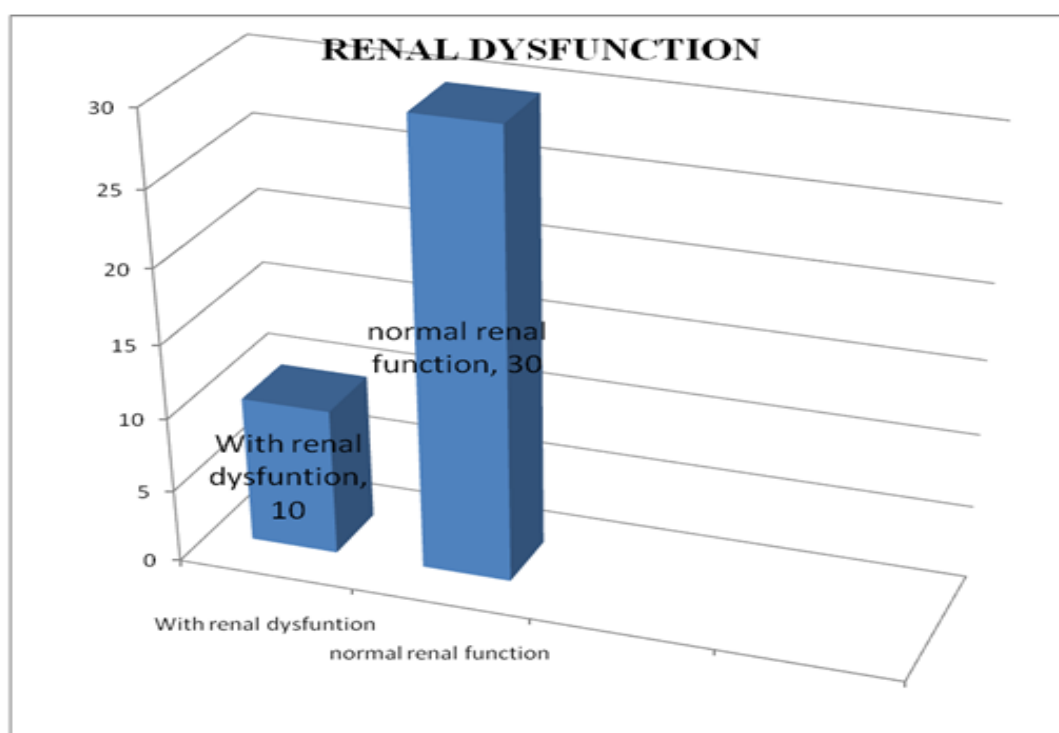


Fig 5 – distribution of renal disease

Table 5 – Distribution of Glycaemic control

Glycaemic control	No of patients
Strict glycaemic control	26
Moderate glycaemic control	14

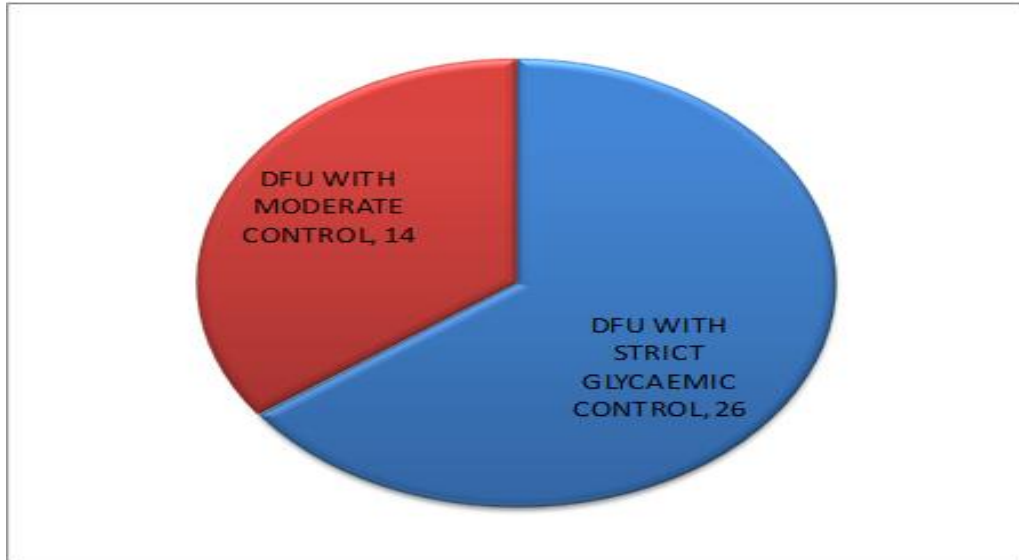


Fig 6 – distribution of glycaemic control

Table 6 – Distribution of Grades of Ulcer

GRADES OF ULCER	No of patients
GRADE 1	1
GRADE 2	10
GRADE 3	17
GRADE 4	12

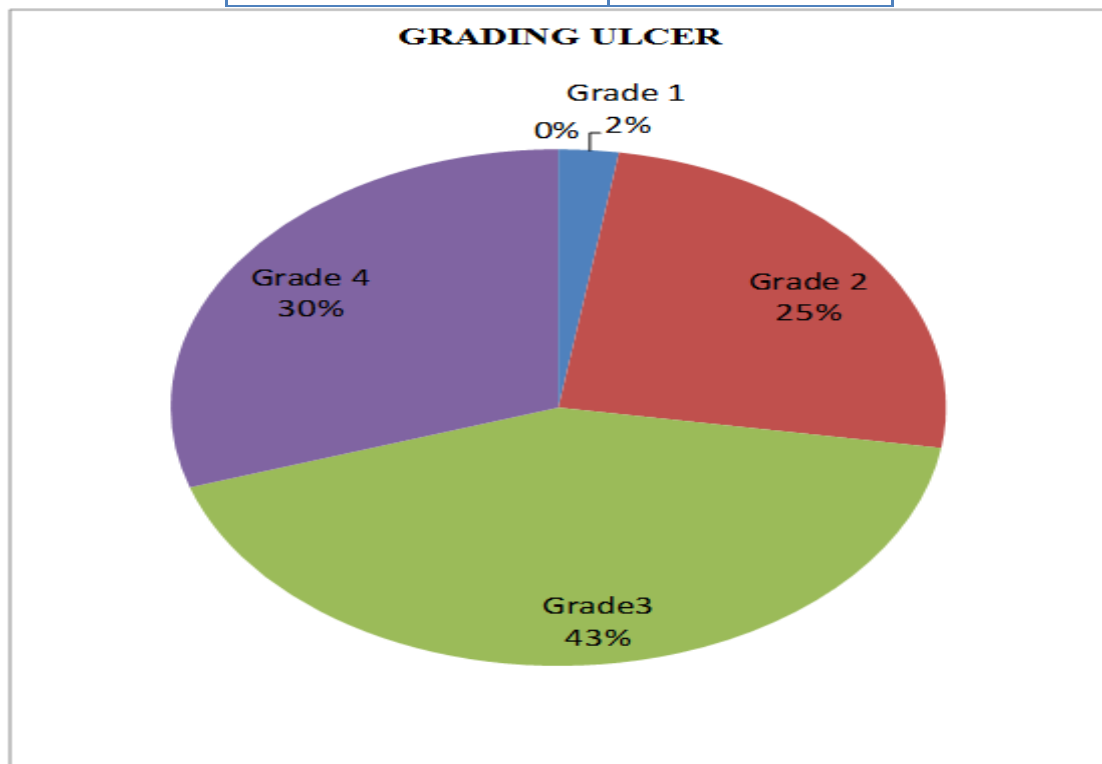


Fig 7 – distribution of grades of ulcer

Table 7 – Distribution of Sites of Ulcer

SITE OF ULCER	No of patients
PLANTAR	10
DORSAL	7
HEEL	4
PLANTAR AND DORSAL INVOLVEMENT	19

Fig 8 – distribution of sites of ulcer

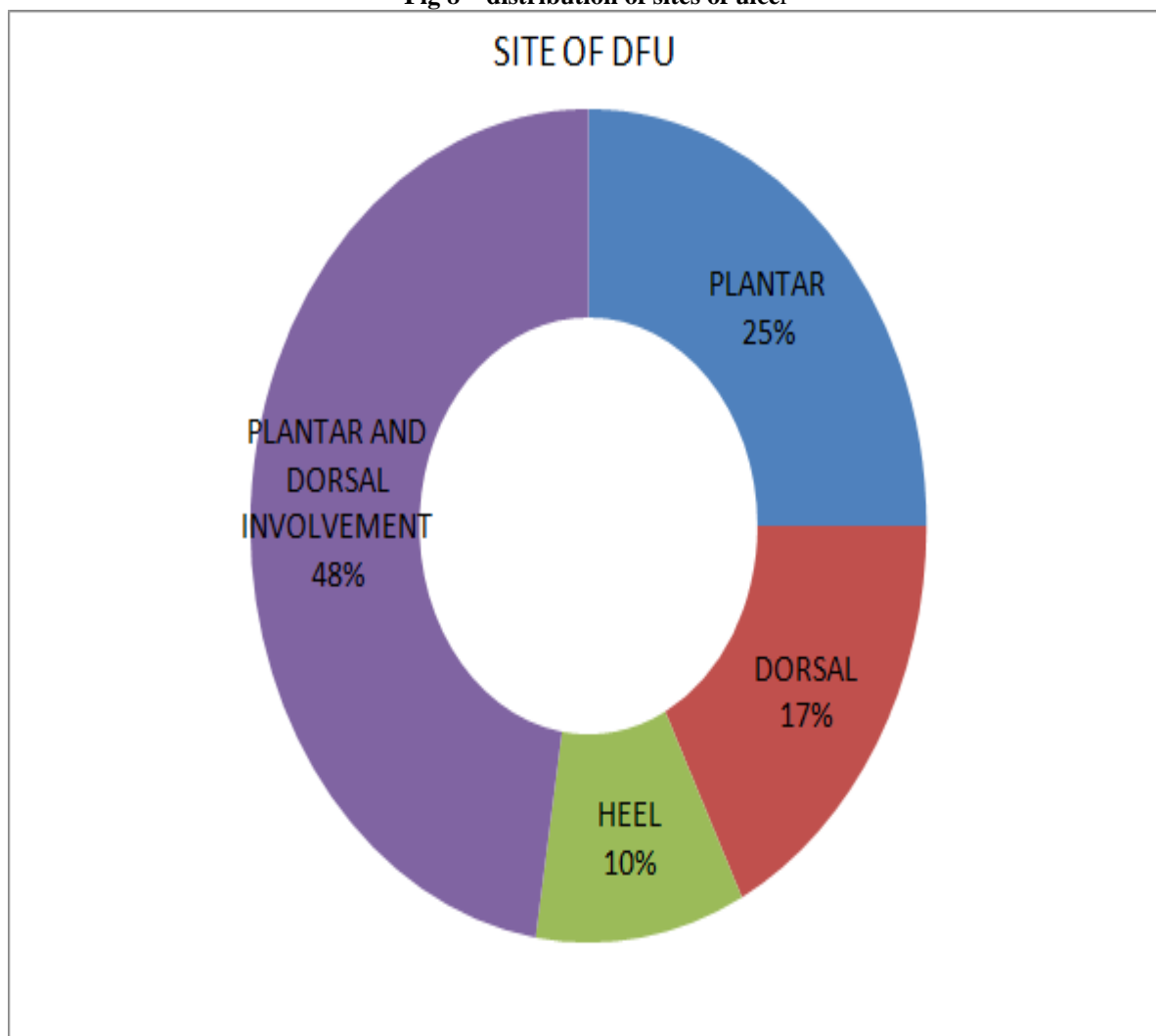


Table 8 – Organisms isolated from swab culture

Organism isolated	No of persons
PROTEUS	18
E.COLI	10
STAPHYLOCOCCI	8
PSEUDOMONAS	4

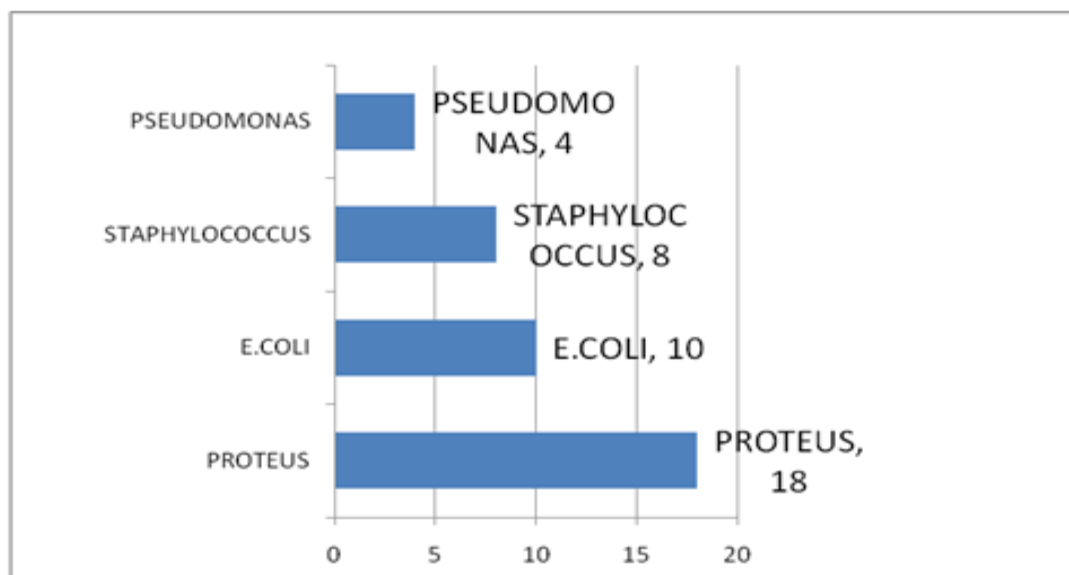


Fig 9 – organisms isolated from swab culture

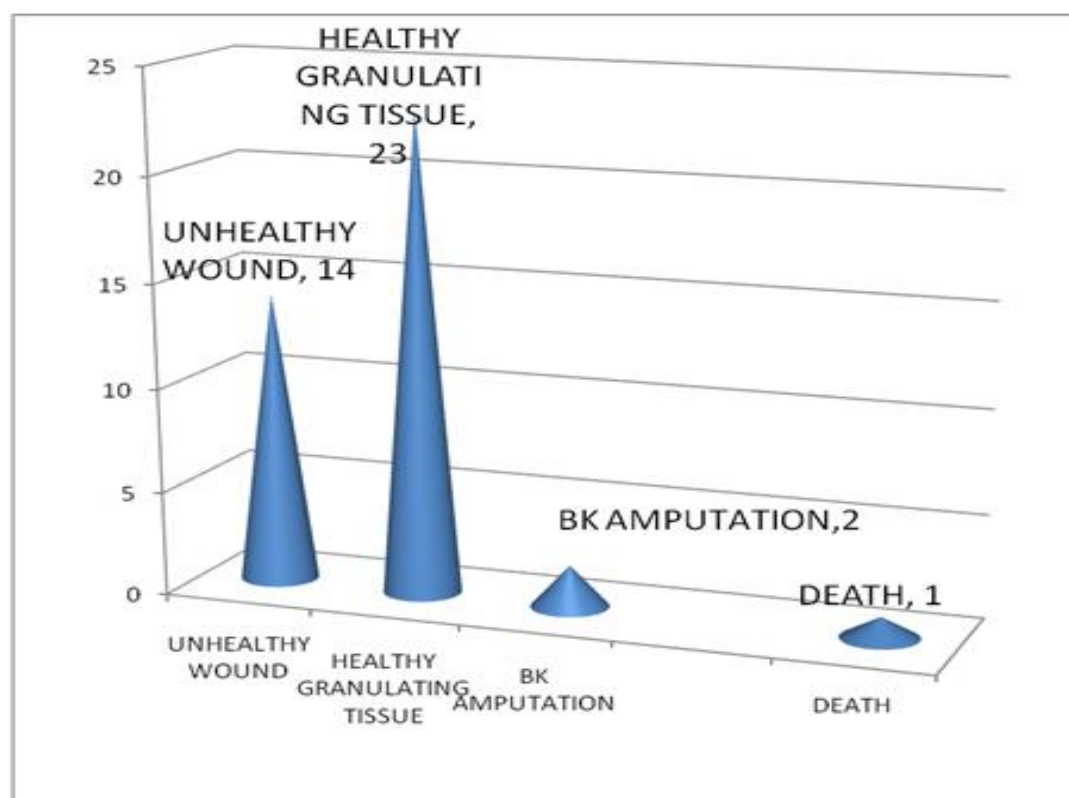


Fig 10 – end results after two weeks

Table 9 – Regression of pain

Assesement day	Treatment group	Severe pain	Bearable pain	No pain
Admission day	Phenytoin gp	16	4	0
	Control gp	15	5	0
Day 7	Phenytoin gp	9	10	1
	Control gp	12	8	0
Day 14	Phenytoin gp	6	6	8
	Control gp	8	10	2

Table 10 – Clearance of Ulcer Discharge

Assesement day	Treatment group	Purulent discharge	Serous discharge	No discharge
Admission day	Phenytoin gp	17	3	0
	Control gp	16	4	0
Day 7	Phenytoin gp	10	9	1
	Control gp	14	6	0
Day 14	Phenytoin gp	2	12	6
	Control gp	8	10	2

Table 11 – Wound culture and Development of Granulation Tissue after 2 weeks

Assesement day	Wound C&S	Phenytoin gp	Control gp
Admission day	Positive for organisms	20	20
End of 2wks	No growth in culture	11	6
Assesement day	Presence of healthy granulation tissue	Phenytoin group	Control group
Admission day	Yes	0	0
	No	20	20
Day 7	Yes	7	4
	No	13	18
Day 14	Yes	12	8
	No	8	12

VI. CONCLUSION

In my study at Govt Rajaji Hospital and Madurai Medical College on topical phenytoin in diabetic foot ulcers these are the following findings in statistical analysis

- DFU is common in the age group of 60-70 yrs
- DFU is common in males
- DFU was common in patients with the duration of diabetes 5- 10 yrs.
- DFU occurs not only in bare foot walkers but also in patients wearing footwear. In our study the later patients were common
- 25% patients were having elevated renal parameters
- 62% had strict glycaemic control
- >70% belong to WAGNER's grade 3 and 4 ulcer
- >50% patients had plantar involvement
- the predominant microorganism on culture was gram negative –Proteus and E.Coli
- On topical application of phenytoin
 - there was significant decrease in pain(but this was more subjective
 - there was decrease in purulent discharge at the end of 1 week
 - significant negative culture at end of 2 weeks
 - there was early formation of granulation tissue

But these findings have to be statistically confirmed.

Contrary to what is seen in the developed world in our environment the lower limb is often vulnerable to trauma and the lack of appropriate management including resting the limb leads to chronic ulcer. Infection and poor circulation contribute to the chronicity of the ulcer. Most patients who present either grade 3 or grade 4 ulcers had a history of ulcer for few weeks and hence proper patient education could have averted severe forms of ulcer.

Topical phenytoin has a role in the healing of diabetic ulcer by decreasing the pain and decreasing the purulent discharge and early formation of granulation tissue.

Whatever the treatment applied thorough surgical debridement and glycaemic control remain the cornerstones in the treatment of Diabetic Foot Ulcers. Considering phenytoin in accelerating wound healing it can be used as a safe, effective easy to use and inexpensive management in the treatment of Diabetic Foot Ulcers.

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***Corresponding Author: Elamaran. E**

¹**Asisstant Professor, Department Of General Surgery, Govt. Rajaji Hospital, Madurai, India**