

# Efficiency of Topical Phenytoin on Healing in Diabetic Foot Ulcer: A Randomized Controlled Trial

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## Abstract

**Introduction:** One-third of patient with diabetic seek hospital admission due to a diabetic foot ulcer. About 15% of diabetic patients will have foot amputation following diabetic ulcer.

**Objective:** The objective of this study was carried out to assess the efficiency of tropical application of phenytoin powder on healing in diabetic foot ulcer Category I and II.

**Materials and Methods:** Totally, 60 patients with diabetic foot ulcer attending the Government Medical College Hospital are randomized into two groups, assigned regular saline and betadine dressing for the control group and phenytoin powder application for the study group. Patient with vascular impairment (or) uncontrolled diabetes are not included. Both the control and study group are compared for the reduction in the slough, granulating tissue formation, pain, duration of hospital stay mean surface reduction of ulcer, to assess the healing process.

**Results:** The wound healing was assessed by the formation of granulation tissue, decrease in the slough and wound size at weekly interval. At the end of 14 days, the presence of healthy granulation tissue were markedly noted in 60% of study group with phenytoin, and it was present only in 10% of control group. Moreover, also wound reduction was 66% in the study group, and 44% in control group. Mean duration of time in the hospital is also significantly reduced in phenytoin group. Pain score was also good in the study group.

**Conclusion:** Based on this study cut come and literature review, we conclude phenytoin sodium powder tropical application on diabetic foot ulcer promotes early wound healing.

**Key words:** Diabetic foot ulcers, Granulation tissue, Tropical phenytoin, Wound healthy

## INTRODUCTION

Diabetes is becoming a disease of modern world and India is marching toward to be the capital of diabetes. India has more than 62 million diabetic individuals. In the world, 7% of the population have diabetes. India is followed by China and USA on the top ranking diabetic country list.<sup>1</sup>

Diabetic foot syndrome is a most common and preventable complication of diabetes. About 15% of

diabetic individual will develop diabetic foot syndrome in their life time.<sup>2</sup> Diabetic foot ulcer precedes 85% amputation in individuals with diabetics. This can be related to many social and cultural patterns in India such as walking with bare foot, lack of knowledge and facility for adequate diabetic care, poverty, and other socioeconomic conditions.<sup>3</sup>

Various therapeutic methods are applied for the healing of diabetic ulcer such as honey, placental gel, vacuum assisted devices, epidermal growth factor cream, and betadine dressing; and each has its own positive and negative factors. Delay in wound healing causes economic burden to the individual and family.

In 1908, the 5-5 diphenyl-2-4 imidazolidinone sodium with generic name of phenytoin was synthesized and used as antiepileptic drug since 1937.<sup>4</sup>

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Gingival hyperplasia due to connective tissue growth was noted as an unwanted side effect of phenytoin as an anticonvulsant medication.<sup>5</sup>

However, this property of connective tissue growth is presumed to have the advantage of wound healing. Various studies have shown a good result of usage of topical phenytoin in promoting healing of decubitus ulcer,<sup>6</sup> venous stasis ulcers,<sup>7</sup> burns,<sup>8</sup> traumatic wounds,<sup>9</sup> and Hanson's trophic ulcers.<sup>10</sup>

Phenytoin is used as a topical application in many studies on diabetic foot ulcers, and it is found to stimulate the formation of granulation tissue as early as 2-7 days. The phenytoin has antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella*, and *Pseudomonas*.<sup>11</sup>

Phenytoin increases proliferation of fibroblasts, enhances collagen deposition, neovascularization, promotes granulation tissues formation, reduces the collagenase action, and contamination of bacteria.<sup>12</sup>

However, there are some contradictory reports on the use of phenytoin as topical agent.<sup>13</sup>

This study is done to understand and postulate the efficiency of phenytoin, a much cheaper drug readily available in the market, on its property of wound healing in diabetic individuals with Grade I and II ulcer as per Wagner criteria.

## MATERIALS AND METHODS

This study was conducted as a randomized case-control prospective study in the Department of Surgery Kanyakumari Government Medical College Hospital from 2014 January to 2014 December. Totally, 60 patients with diabetic foot ulcers of more than 4 weeks duration without any co-morbid conditions and ulcers belong to Grade 1 and 2 as per Maggot - Wagner diabetic foot ulcers were inducted into the study.

### Ethical Aspects

The study proposal was approved by the Ethical Committee of our Institution. All participants were provided and obtained written informed consent after explaining all the features of the study.

### Diabetic Foot Ulcer Wagner Classification

Grade 0 → No risk

Grade I → Superficial ulcers

Grade II → Deep ulcers

Grade III → Deep ulcers with abscess

Grade IV → Gangrene - Limited

Grade V → Gangrene - Extensive

Inclusion criteria:

- Diabetic foot ulcer more than 4 weeks of Grades I and II with fasting blood sugar 110-130 mg/100 ml on two consecutive days
- Age group 18-80, both male and female
- Consent for inclusion in the study.

Exclusion criteria:

- Diabetic ulcer with Grades III, IV, V
- Uncontrolled diabetics
- Presence of vascular impairment
- Presence of osteomyelitis
- Associated co-morbidity such as hepatic and renal diseases
- Patient on steroids
- Nonwilling patients.

### Ethical Concerns

The study proposal was approved by the Ethical Committee of our college. All the patients included in the study were explained all the factors of this study and their informed written consent obtained.

### Sample Selection and Grouping

Using the World Health Organization, sample size calculated with the values of 5% as the level of significance and 90% as the power of the test. The inducted patients were divided into two equal groups randomly using lottery method. A total of 30 patients inducted as a study group for the use of topical phenytoin powder, and the rest 30 were followed with a classical wound dressing with p-iodine and saline wash with magnesium sulfate dressing are taken as a control group.

### Procedure

Phenytoin powder is prepared from the capsule and amount of powder application depends upon the surface area of the diabetic foot ulcer.

Up to 5 cm → 100 mg

5-9 cm → 150 mg

9-15 cm → 200 mg

>15 cm → 300 mg

The foot ulcers are adequately cleaned with hydrogen peroxide-saline-betadine solution.

Phenytoin sodium capsule was opened and placed in 5 ml of normal sterile saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound as a thin layer culture of wound done on induction and antibiotics are given to both the groups as per culture reports. Daily monitoring of blood sugar appropriate treatments are provided.

In the well cleaned and debrided wounds, the surface area of the ulcer is measured on day 1 using tissue paper

mapping. The proper wound care and phenytoin powder application is carried out daily. The wound is assessed in terms of healing shown by the reduction in surface area, formation of granulation tissue, amount of discharge, microbiological status, and pain factor by a blind observer at the end of every week and to the maximum of 6 weeks.

**Statistical Analysis**

Chi-square test was used. The observer was calibrated by using Kappa coefficient (0.6)

**RESULTS**

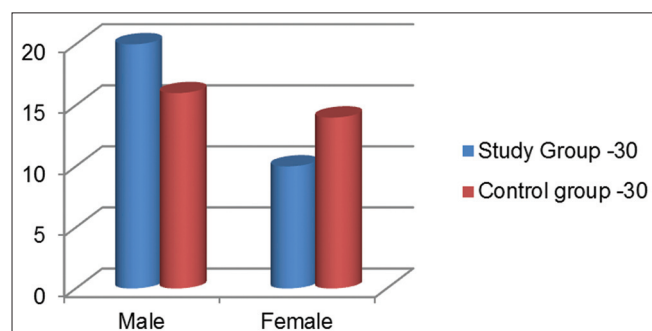
A demographic study of patients inducted into our study shows age ranges from 18 to 80. However, the majority of cases are from the age group of 51-70.

The mean age of study group was 52.63 ± 7.1 and the control group was 53.1 ± 6.83. Male constitute 60% of the inducted patients and female 40%. Age and gender distribution were similar between each group, P = 0.413 for age and P = 0.578 for male and female difference. Hence, it is proved the demographic variations cannot influence the efficiency of the treatment. The sites of the presence of an ulcer in each group were also studied. The findings are tabulated in Table 1 and Figures 1 and 2.

The surface area of the ulcer predominantly corresponds in each group, and the majority of ulcers were of 9-15 cm size and no significant variations among the group. Pus culture from the ulcer was carried out. The organisms present were

**Table 1: Demographic profile of patient in study/control group**

Variables	Study group (30)	Control group (30)	Significant
Male	20	16	P=0.578
Female	10	14	-
Mean age	52.63±7.1	53.1±6.83	P=0.413
Ulcer in dorsum	14	16	
Ulcer in heal	8	7	
Other site	8	7	



**Figure 1: Demographic profile of patient in study/control group**

tabulated in Table 2 and Figure 3. *S. aureus* was found to be the most common pathogen in both the group.




The reduction in the presence of slough and formation of healthy granulation tissues are assessed on the 14<sup>th</sup> day.

In the study group, with phenytoin use only 6 cases (20%) had slough, but in the control group slough continued to present in 24 patients (80). This is a statistically significant difference (Chi-square =16.4, P < 0.005, df = 1).

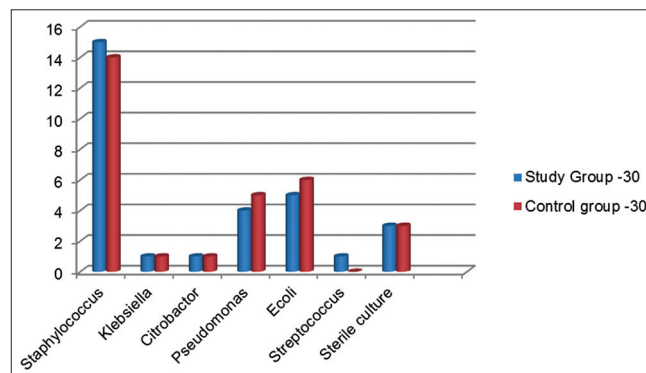
**Table 2: Culture reports in diabetic foot ulcer**

???	Study group (30)	Control group (30)
<i>Staphylococcus</i>	15	14
<i>Klebsiella</i>	1	1
<i>Citrobactor</i>	1	1
<i>Pseudomonas</i>	4	5
<i>E. coli</i>	5	6
<i>Streptococcus</i>	1	0
<i>Sterile culture</i>	3	3

*E. coli: Escherichia coli*

Phenytoin study group	Site of the ulcer	Control group
14	Dorsum of the foot 	16
8	Heel of the foot 	7
8	Other site 	7

**Figure 2: Site of the ulcer in the foot**



**Figure 3: Culture reports in diabetic foot ulcer**

The healthy granulation tissue formation was found in 18 patients (60%) in phenytoin group however, only 3 patient (10%) in the control group has good healthy granulation tissue on day 14. The difference is also statistically significant (Chi-square = 16.8,  $P < 0.005$ ,  $df = 1$ ).

The duration of hospital stay was prolonged in patient in the control group. The mean duration of stay for patient with diabetic foot using phenytoin topical application was 19 days for the control group it is 25 days. This also shows the economic burden on the family.

The reduction in surface area of the ulcer in the patient in a study group with phenytoin use was 66% and in the control group 46% on 21<sup>st</sup> day of therapy. This difference is also statistically significant ( $P = 0.045$ ). The findings are shown in Table 3.

The results of the study on the reduction in the slough, formation of healthy granulation tissue, more than 50% reduction in wound size, and duration of hospital stay as shown, they are significantly different from study group and control group, shows patient with the use of phenytoin has better wound healing parameters.

Study on pain score for ulcer with visual analog scale shows 72% reduction in pain, by the 7<sup>th</sup> day of dressing in phenytoin group and 36% in control group.

## DISCUSSION

All over the world for every 30 s one foot is amputated due to diabetes and 85% this can be prevented if early detection and adequate care is provided at the appropriate time. A variety of treatment modalities is available from the treatment of diabetic foot ulcer. In 1934, Elliot said, "Diabetic gangrene is not heaven sent but is earth-born."<sup>14</sup>

Plethora of research monograph is available on the variety of care for a diabetic ulcer. The adequate wound debridement, appropriate antibiotic coverage, improvement of general well-being of individuals are paramount important for wound healing. Topical phenytoin has proved its worthiness as an inexpensive therapeutic agent in wound healing.

The phenytoin induces growth of granulation tissue, angiogenesis, and decreases wound size.

Mod er and Andersson in 1990, in their study, on regulation of epidermal growth factor receptor metabolism in gingival fibroblasts proved that phenytoin significantly increases epidermal growth factor receptors in the fibroblast resulting in the gingival hyperplasia.<sup>15</sup>

DaCosta *et al.* in 1998, by their experimental study proved phenytoin enhances the fibroblast infiltration with neovascularization and significantly increases the tensile strength of healed wounds.<sup>12</sup>

Anstead *et al.* reported that phenytoin has promoted healing in a massively necrotized Grade IV decubitus ulcer not responding to any other therapy.<sup>16</sup>

Various studies shows phenytoin stimulates proliferation of fibroblasts, significantly increase the receptors of epidermal growth factor and keratinocyte growth factor in the fibroblasts, reduces the activity of collagenase in the wound, accelerate the early inflammatory responses, induce the neovascularization, effectively reduces the burden of infective microbial and there by promotes healing.

Phenytoin has significant antibacterial properties. Pendse *et al.* have proved in their study 50% wounds treated with phenytoin had negative bacterial culture on 7<sup>th</sup> day of treatment, where as in the control group only 17% had negative culture (Figure 4).<sup>17</sup>

Diabetic foot ulcer usually shows a poly microbial infection pattern. However, the most common organism found is Gram-positive cocci. In a multicentric clinical trial conducted in ulcer, Citron *et al.* have shown 83.8% of the cultures are polymicrobial in nature with 48% only aerobic bacteria, 43% mixed with aerobe and anaerobe, and only 1.3% shows anaerobic bacteria.<sup>18</sup>

Our study also proves there are predominantly aerobic Gram-positive and negative organisms, and isolated anaerobes are less in number, more so in new cases. *Staphylococcus* and *E. coli* constitute the major organism group. The phenytoin reduces the organisms and decreases the slough as early as 7 days.

**Table 3: Comparison of ulcer healing parameter in two groups**

Parameters	Study group (30)	Control group (30)	P value
Presence of slough on 14 <sup>th</sup> day (%)	6 (20)	24 (80)	<0.005
Presence of healthy granulation tissue on 14 <sup>th</sup> day (%)	18 (60)	3 (10)	<0.005
Duration of hospital stay	19 days	25 days	<0.005
Percentage of reduction in ulcer area (%)	66	46	<0.045
Efficiency as more than 50% reduction of ulcer (%)	21 (70)	12 (40)	0.041





**Figure 4: Progression and response to phenytoin therapy,(a) On admission (b) On 7<sup>th</sup> day (c) On 14<sup>th</sup> day**

Many authors including Chincholikar and Pal, have shown the most common Gram-positive organisms are *S. aureus* and *Pseudomonas aeruginosa*. The most common anaerobes are *Bacteroids fragilis*. Our study also shows increased percentage of *Staphylococcus* and *Pseudomonas*.<sup>19</sup>

The antibacterial property of phenytoin is manifested both as an intrinsic activity and also mediated by the effect of phenytoin on inflammatory cell and its property to induce neovascularization.<sup>20</sup>

Reduction on the wound surface area is the marked feature of phenytoin use. Pai *et al.* in their double blind control study on phenytoin in neuropathic diabetic foot ulcer demonstrated 78% of wounds treated by phenytoin had more than 50% reduction in the ulcer size.<sup>21</sup>

In our study, also 70% in the phenytoin group shows more than 50% reduction while only 14% of patient in the control group shown more than 50% reduction of the size.

Another advantage of phenytoin observed is the reduction in the pain score of the ulcer. The study shows a significant reduction in the pain score of the patient from 7<sup>th</sup> day resulting in less use of analgesia. This is explained by the effect of phenytoin on the membrane stabilizing property and its ability to reduce the inflammatory response.<sup>22</sup>

In a comparative study, of EUSOLVs phenytoin on the diabetic foot ulcer conducted by Carneiro and Nyawawa in 100 patients proved that phenytoin use has resulted in significant reduction in the pain score and quantity of ulcer discharge.<sup>23</sup>

Shaw *et al.* done a systematic review of role of phenytoin as topical agent in the healing of diabetic ulcers using PubMed, Medline, and Cochrane database with 14 available randomized controlled trials and concluded that use phenytoin has moderate evidence to confirm and support the use of phenytoin as topical therapeutic agents in not only diabetic ulcers but also varicose leg ulcers and necrotic wounds.<sup>24</sup>

Pitiakoudis *et al.* in their experimental study on pressure ulcer in a paraplegic person stated phenytoin enhances

faster healing by stimulating lymphocyte chemotaxis and super regulation of angiogenesis.

Phenytoin is considered a safe, inexpensive, and effective in wound healing by several researchers.

## CONCLUSION

This prospective randomized control study shows enhanced wound healing and sense of well-being in individuals with diabetic foot ulcer treated with topical application of phenytoin than the other classical wound dressing materials.

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