## **Original Research Article**

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# The efficacy of phenytoin dressing in healing of diabetic ulcer: a randomized control study

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#### **ABSTRACT**

**Background:** Diabetic foot infection constitutes up to 10 percent of diabetes-related hospital admissions and the prevalence of diabetes is 2.4% in rural and 12-17% in urban settings. The quest for better wound healing agents for diabetic ulcers is perhaps one of the oldest challenges for medical practice. One such agent that has been tried in wound healing is phenytoin. A common side effect of phenytoin (diphenylhydantoin) treatment for epilepsy is gingival hyperplasia. This stimulatory effect of phenytoin on connective tissue suggested a possibility for its use in wound healing.

**Methods:** 60 patients with diabetic foot ulcer admitted in General Surgery at Mahatma Gandhi Medical College and Research Institute, Puducherry, India were randomly assigned into two groups, the study group consisting of 30 patients who were treated with phenytoin dressing and 30 patients into control group who were treated with conventional saline dressing. Both groups underwent initial debridement and were started on parenteral antibiotics according to wound swab culture and sensitivity. Study group were treated with phenytoin dressing and the wound was assessed based on the rate of ulcer size reduction, the rate of granulation tissue, duration of hospital stays and antibacterial property of phenytoin. Patients were assessed weekly up to 21 days.

**Results:** The rate of granulation tissue in phenytoin group was 90.36% which was statistically significant (p = 0.0011) as compared to control group which was 82.03%. Wound swab cultures repeated on day 21 revealed that there was 50% negative culture in phenytoin group when compared to control group of 24% which also was statistically significant. The mean hospital stay for the patient in phenytoin group was 29.2 days and in control group, it was 26.1 days. It was observed that surface area reduction in phenytoin group was 41.25cm<sup>2</sup> to 18.38cm<sup>2</sup> and in control group was 40.28cm<sup>2</sup> to 20.23cm<sup>2</sup> by the end of 21 days, but this was not statistically significant.

**Conclusions:** Phenytoin dressing is effective in increasing the rate of granulation tissue by virtue of its action on stimulating fibroblast proliferation and decreasing collagenase activity. It not only hastens granulation tissue but also decreases bacterial load as compared to conventional dressing by virtue of its intrinsic antibacterial activity and indirectly through their effects on anti-inflammatory cells and neovascularization. Phenytoin prepares the foot ulcer for early grafting thereby improving the overall outcome.

**Keywords:** Diabetic foot ulcer, Granulation tissue, Moist dressing, Topical phenytoin dressing, Wound healing

#### INTRODUCTION

In India, diabetic foot infection constitutes up to 10 percent of diabetes-related hospital admissions and the

prevalence of diabetes is 2.4% in rural and 12-17% in urban.<sup>1</sup> Almost 40,000 legs are amputated every year as a result of infected, neuropathic foot in India.<sup>2</sup> The risk of losing a limb is 25 times higher in diabetes mellitus than

other illness. Non- healing (or) chronic diabetic wounds are a significant health care problem of today's practice as its healing depends on many factors such as glycemic control, vascularity, bacterial load, the location of the wound and nutritional status of the patient.<sup>3,4</sup> Many agents have been tried in wound healing; the quest for better wound healing agent is perhaps one of the oldest challenges for medical practice. The phenytoin, a common anticonvulsant also has been tried in wound healing. It was introduced into therapy in 1937 for the effective control of convulsive disorders.<sup>5,6</sup> Studies have shown topical phenytoin to promote healing of decubitus ulcers, venous stasis ulcers, traumatic wounds, burns and leprosy trophic ulcers.7-13 A common side effect of phenytoin (diphenylhydantoin) is gingival hyperplasia see during treatment of epilepsy. 14 This stimulatory effect of phenytoin on connective tissue suggested the possibility for its use in wound healing. The mechanisms of action of Phenytoin involved in the healing process are at several levels including stimulating fibroblast proliferation, enhancing the rate of formation of granulation tissue, reducing collagenase activity, hastening deposition of collagen, decreasing bacterial load and decreasing wound exudates. 15-19 The present study was conducted to assess the efficacy of topical phenytoin dressing as compared to conventional moist wound dressing (saline) in the healing process of diabetic ulcers and to check whether it is a better alternative in the management of diabetic ulcers.

## **METHODS**

This study was conducted at Mahatma Gandhi Medical College and Research Institute, Puducherry, a tertiary care hospital. The aim of the study was to find the efficacy of topical phenytoin compared to conventional wound care (saline) in the management of diabetic foot ulcer in terms of rate of granulation tissue formation, the rate of ulcer size reduction, the number of days for wound healing and serial culture and sensitivity of wound swabs to assess the antibacterial effect. It was a randomized prospective study wherein 60 patients with diabetic foot ulcer were computer randomized into two groups of thirty each. The Institutional Human Ethics Committee has approved this study. An informed consent was obtained from each patient recruited for this study after explaining the nature of the study and the possible investigations involved in the study.

Patients admitted with a non-healing diabetic foot ulcer, Diabetic ulcer grade I and II (Wagner clinical classification) were included in this study. Patients with grade III and above, chronic non-healing wounds of other aetiology, diabetes mellitus with gangrenous changes, wounds with osteomyelitis, wounds with poor vascularity determined by peripheral pulses/ hand Doppler and other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing were excluded from this study. Patients with previous history of phenytoin intake were also excluded

from this study. A total of 60 patients were enrolled between December 2014 to May 2016 for the study. After admission, a complete history of the patients was obtained regarding the mode of ulcer, its progression, duration and type of diabetes, type of medication the patient is taking and associated co-morbidities. Then a complete physical examination was carried out including peripheral arterial examination with a hand-held Doppler. Routine pre-operative baseline investigations were done in both the groups.

#### Inclusion criteria

- Patients admitted with non-healing diabetic foot ulcer
- Diabetic ulcer grade I and II (Wagner clinical classification).

#### Exclusion criteria

- Patients with diabetic ulcer grade III and above
- Chronic non-healing wounds of other etiology
- Diabetes mellitus with gangrenous changes
- Wounds with osteomyelitis
- Wounds with poor vascularity determined by peripheral pulses/ Hand Doppler
- Other co-morbid conditions like renal failure, generalized debility and other factors, which adversely affect wound healing.

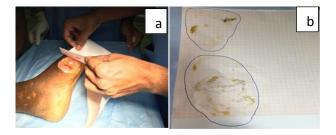


Figure 1: (a and b) Measurement of ulcer size using graph paper with grids.

All subjects fulfilling the inclusion criteria were computer randomized into two groups of thirty each. Patients receiving Phenytoin dressing were considered as a study group and those receiving conventional normal saline dressing were considered as a control group. Prior to application of phenytoin or saline dressing, thorough surgical debridement was done in all patients to remove all necrotic tissues and slough and adequate haemostasis was achieved. On admission, wound swab for culture and sensitivity was sent. Patients were started on parenteral antibiotics as per the sensitivity pattern.

For study group, after cleaning the wound bed with antiseptic, a single 100 mg phenytoin sodium ampule was opened and mixed in 5 ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound. The required concentration of phenytoin was measured based on ulcer size, 0-5 cm<sup>2</sup> 100

mg, 5.1-10 cm² 150 mg, and 10.1-15 cm² 200 mg, respectively. For the control group, after cleaning the wound bed with antiseptic, gauze soaked with saline was applied. Dressings were changed on alternate days in both groups. Wounds were assessed based on ulcer size and granulation tissue on Day 1, 7, 14 and 21. Ulcer size and granulation tissue was measured using planimetry (grid tracing on graph paper Figure 1). wound swab for culture and sensitivity pattern was repeated on Day 21. All data were entered into excel program in which analysis was done. Standard guidelines were adhered for analysing the data.

#### RESULTS

Out of 60 cases studied there was male predominance in the occurrence of diabetic foot ulcers, 63.3% were male and 36.7% were female. Most of the diabetic foot patients were in the age group of 30-49 years (50%) and mean age presentation to our hospital was 46 years (Figure 2). The youngest was 25 who came with ulcer over the sole. The most common presentation of diabetic foot ulcers was in dorsum (31%), sole (19%), leg (21%), toes (20%), around Ankle joint (8%). Most of the patients had haemoglobin in the range of 7-10%. The mean haemoglobin in the study group was 9.5% and in control group was 8.4%. Most of the patients had an HbA1C in the range of 7.1-10. The mean HbA1C in the study group was 9 and in control group was 8.9 (Table 1).

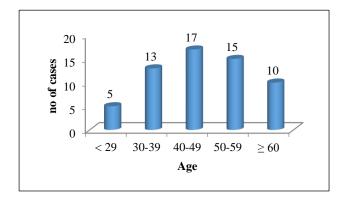


Figure 2: Age distribution.

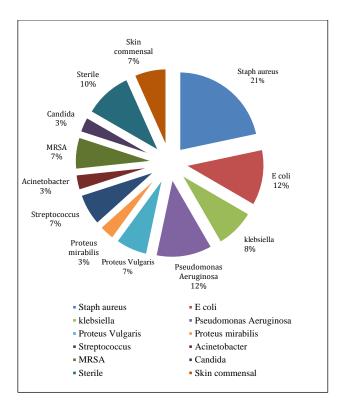


Figure 3: Microbiological study.

A Total of 60 microorganisms were cultured among which Staphylococcus Aureus, E coli, Klebsiella, Pseudomonas Aeruginosa species were most common organisms causing diabetic foot ulcer (Figure 3). Out of 30 cases in study group 26 patients culture showed growth and 2 patients culture showed skin commensals and 2 patients culture was sterile on day 1. Out of 26 growths, 13 cultures were sterile by the end of 21 days in the study group. Similarly, in control group 25 patients culture showed growth and 1 patient skin commensals and 4 patients culture was sterile on day 1. Out of 25 growths, only 6 cultures were sterile by the end of 21 days. It was observed that there was 50% conversion of a negative culture in the study group when compared to 24% in control group, reflecting the antibacterial action of phenytoin.

Table 1: Comparison	of different	parameters be	tween study ar	nd control group.

Parameters	Study		Control	
Age	43.83 (Years)		50.03 (Years)	
Haemoglobin	9.56 (%)		8.4 (%)	
Hba1c	8.6		8.7	
Duration of stay	26.1 (days)		26.1 (days)	
Percentage negative culture	50 (%)		24 (%)	
	Day 1	Day 21	Day 1	Day 21
Rate of granulation	26.8 (%)	90.36 (%)	25.27 (%)	82.03 (%)
Surface area	41.25 (cm <sup>2</sup> )	18.38 (cm <sup>2</sup> )	41.28 (cm <sup>2</sup> )	20.23 (cm <sup>2</sup> )

The duration of the hospital was prolonged in control group when compared to study group. The mean duration of stay for phenytoin group was 26.1 days and 29.2 days for the control group. The rate of granulation tissue formation was 90.36% in phenytoin group and 82.03% in control group by the end of 21 days. It was observed that surface area reduction in phenytoin group was 41.25cm<sup>2</sup> to 18.38cm<sup>2</sup> and in control group was 40.28cm<sup>2</sup> to 20.23cm<sup>2</sup> by the end of 21 days (Figure 4).

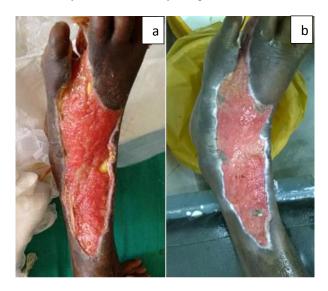


Figure 4: (a) Study group; Diabetic foot ulcer over the dorsum of the foot on day 7; (b) Same patient on day 21.

#### DISCUSSION

Foot ulcers are commoner in diabetic patients with a prevalence of 25% and cause major morbidity and mortality to the society.<sup>20</sup> Phenytoin has been widely used in the treatment of epilepsy since 1937. It has been used for the treatment of various diseases. Adverse effects like allergy, the proliferative idiosyncratic cutaneous lesion has been reported.<sup>5</sup> Phenytoin is also used for non-healing

ulcer like decubitus ulcers (el Zayat, Rhodes et al), venous stasis ulcers (Simpson et al), traumatic wounds (Modaghegh et al, Pendse et al), burns (Lodha), leprosy trophic ulcers (Bansal and Mukul). A study conducted by Sankar et al, showed that application of phenytoin has increased the rate of granulation and increased graft uptake in diabetic foot ulcer.<sup>21,22</sup>

**Table 2: Age wise distribution.** 

	Patil V et al <sup>23</sup>	Present
Control	49.74	50.03
Study	48.5	43.83

The most common period of presentation in our study was 45-50 year which is similar to the study conducted by V. Patil et al (45-50), showing that diabetic foot ulcer usually occurs in old ages.<sup>23</sup> (Table 2) Like Muthukumarasamy et al, study the present study also showed that more number of male patients suffer from diabetic foot ulcer.<sup>24</sup> The current study had male: female ratio of 2:1 (Table 3). The present study showed the extensive involvement of dorsum of foot, sole and toes when compared to study by Apltqvist J et al, which showed the extensive involvement of toes and sole (Table 4).<sup>25</sup>

**Table 3: Sex wise distribution.** 

Sex	Muthukumarasamy et al <sup>24</sup>	Present
Male	54	38
Female	46	22

**Table 4: Comparison of site of the lesion.** 

Site of the lesion	Apltqvist J et al <sup>25</sup>	Present
Leg	-	13
Dorsum of foot	19	14
Sole	28	11
Toes	51	12

Table 5: Comparison of duration of hospital stay.

Variable	Tauro LF <sup>22</sup>		Raj R <sup>29</sup>	Raj R <sup>29</sup>		Rao S <sup>21</sup>		Present	
	Study	Control	Study	Control	Study	Control	Study	Control	
Duration of stay	32.26	54.00	32.21	38.76	30.04	45.10	26.1	29.2	

The study conducted by Nouvong A et al showed that cutaneous oxygenation strongly correlates with diabetic wound healing. In our study, most of the patients had low haemoglobin according to their sex with a mean value 9% and hence low tissue oxygen concentration.<sup>26</sup> It has been well established that there is a strong correlation between wound healing and HbA1C. According to NICE guidelines, the HbA1C should be maintained in the range

of 6.5 to 7 for better wound healing.<sup>27</sup> Our study showed that HbA1C among our population is in the range of 8.4 to 9.5 which reflects uncontrolled diabetes leading to prolonged wound healing.

Culture from diabetic foot ulcers is usually polymicrobacterial. A study conducted by Citron et al showed that aerobic bacteria (48%) are usually cultured in diabetic wounds. Our study also showed a similar

result of *Staphylococcal Aureus* (21.7%) and *E Coli* (11.7%). Large numbers of studies have shown that phenytoin reduces the bacterial load on diabetic ulcer by 7 days due to their intrinsic antibacterial activity and indirectly through their effects on anti-inflammatory cells and neovascularization.<sup>28</sup> The antibacterial activity of phenytoin has been reflected in our study also with 50% negative culture by the end of 21 days in the study group

when compared to 24% in control group. Gram positive cocci were the predominant isolates in our study. We also isolated good number of aerobic gram-negative organisms. There have been similar reports from studies which were done in north India. The isolation rate of aerobic gram-negative bacilli was relatively less in many of the western reports.<sup>23</sup>

Table 6: Comparison of granulation tissue.

Variable	Tauro LF <sup>22</sup>		Raj R <sup>29</sup>		Rao S <sup>21</sup>	Rao S <sup>21</sup>		Present	
	Study	Control	Study	Control	Study	Control	Study	Control	
Rate of granulation	87.94	74.64	88.21	71.32	85.21	70.32	90.36	82.03	

The duration of hospital stay was also reduced in the study group (26.1) compared to control group (29.2) which was almost similar to other studies like Tauro LF et al, Raj R et al, Kodela SR et al. 21,22,29 This reduces the economic burden to the patient (Table 5). Various studies have shown that phenytoin enhances wound healing by stimulating fibroblast proliferation, enhancing granulation tissue, decreasing collagenase activity (by reducing its production or secretion or both), promoting deposition of collagen and other connective tissue components.4 A study conducted by Tauro LF et al, Raj R et al, Kodela SR et al showed that phenytoin increase rate of granulation tissue formation to 87% in the study group when compared to 72% in control group by the end of their study. 3,4,29 A similar increase in the rate of granulation was observed in our study of 90% in phenytoin group and 82% in control group which is statically significant with a p value of 0.0011 (Table 6). Similarly, there was a decrease in surface area of ulcer from 41.25 cm<sup>2</sup> to 18.38cm<sup>2</sup> in the study group and 40.28 cm<sup>2</sup> to 20.23 cm<sup>2</sup> in control group. But this was not statistically significant in our study.

#### **CONCLUSION**

Phenytoin dressing is effective in increasing the rate of granulation tissue by virtue of its action on stimulating fibroblast proliferation and decreasing collagenase activity in wound surface. It not only hastens granulation tissue but also decreases bacterial load as when compared to conventional saline dressing by virtue of its intrinsic antibacterial activity and indirectly through their effects on anti-inflammatory cells and neovascularization. Phenytoin prepares the foot ulcer for early grafting thereby improving the overall outcome. In our present study, it was concluded that the rate of granulation tissue formation was significant in topical phenytoin dressing group as compared to conventional dressing group. It was also seen that the overall hospital stay was less in the topical phenytoin dressing group. But there is no significant overall rate of reduction of ulcer size in both groups. Thus, topical phenytoin moist wound dressing

can be considered as a superior option in the management of diabetic ulcers.

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