

## Original Research Article

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# A comparative analysis of the efficacy of topical phenytoin with conventional wound dressing in healing of diabetic foot ulcers

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## ABSTRACT

**Background:** Foot ulcers secondary to diabetes mellitus are very difficult to treat. Various agents have been used with varying success for their treatment. Recently phenytoin has been used in the treatment of these stubborn ulcers. Therefore this study was conducted and compared for the efficacy of topical phenytoin with conventional wound dressings in healing of diabetic foot ulcers.

**Methods:** This is a prospective study comprising of 50 patients which were divided into two groups. In group I patients conventional betadine dressing was applied. In group II patients phenytoin was used for the dressing. Both the groups were compared on various parameters like time required for healing, complications, grafting and the results were statically evaluated.

**Results:** Increased rate of granulation tissue formation was seen in topical phenytoin group when compared to conventional group. Better graft take up was seen in topical phenytoin group when compared to conventional group. On contrasting the number of days required for healing, effect on bacterial load and side effects of topical phenytoin dressing with conventional betadine dressing, the former yielded better results in all respects.

**Conclusions:** Topical phenytoin dressing is an effective, inexpensive and widely available therapeutic agent in wound healing in chronic diabetic ulcers.

**Keywords:** Diabetic foot ulcers, Grafting, Phenytoin, Topical

## INTRODUCTION

Chronic wounds, especially non-healing types are one of the most common surgical conditions encountered by a surgeon. The peculiarity of a chronic wound is that despite of daily dressing with expensive local applications, the wound does not heal. This problem is especially seen in diabetic ulcers, venous ulcers and pressure ulcers. Thus, to treat such wounds is a constant challenge for the surgeon. The notion that wounds should be kept dry, although still held by a considerable number of surgeons, is steadily losing ground. We now know that wounds develop granulation tissue when treated with dressing which allow moist wound healing. During the last two decades a wide variety of innovative dressings

have been introduced. Various non-conventional topical therapies in wound healing have been tried. Recently some studies have shown that topical phenytoin promotes healing of decubitus ulcer, venous ulcer, pressure ulcer & leprosy ulcer and was found to be of superior in the management ulcers of diabetic.<sup>1-3</sup> We therefore conducted this study to evaluate the efficacy of topical phenytoin in healing of diabetic ulcers and its comparison with other dressings.

## METHODS

This is a prospective randomized comparative study which was conducted at a tertiary level health care center. A sample size of 50 patients has been taken for the

present study and sampling technique used was purposive sampling. The patients were divided into two groups (a) betadine group (n=25), and (b) phenytoin group (n=25).

#### Inclusion criteria

Grade I and II foot ulcers according to Meggit-Wagner clinical classification and patients with controlled diabetes mellitus with oral hypoglycemic agents or insulin.

#### Exclusion criteria

Grade III, IV, V foot ulcers according to Meggit-Wagner clinical classification chronic ulcer of other etiology.<sup>4</sup> Any other co morbid conditions like renal failure, generalized debility which adversely affect wound healing and patients with allergy to phenytoin

Data was collected using customized proforma specially designed for the purpose of the study. A sample of 50 patients was selected. At the time of enrollment, a written informed consent was obtained. All patients underwent general physical and clinical examination for peripheral vascular status and peripheral neuropathic changes in lower extremities. Routine hematological, biochemical, urine microscopic investigations were done for each patient.



**Figure 1a: Ulcer before phenytoin dressing (SL-slough).**



**Figure 1b: Ulcer after phenytoin dressing (GT- granulation tissue).**

The selected patients were randomly assigned (using lottery method) into treatment group and control group. In each patient one ulcer was chosen and surgical debridement was done when necessary (Figure 1a). After slough removal, the surface area was measured, tracing

the outline on butter paper. This outline was transferred to graph paper. On each occasion ulcer areas were measured twice. When identical, the reading was recorded. If not the average was recorded.

#### Preparation for dressing

A single 100mg phenytoin sodium capsule was opened and placed in 5ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound at 20mg/cm<sup>2</sup> of ulcer area (Figure 1b). Conventional dressing was done with 5% w/v povidone-iodine solution. Dressings was done on twice daily basis. The patients were followed up on a daily basis for 14 days in both study and control groups. Wound culture/colony count/tissue culture was obtained at the start of the treatment and on the 7<sup>th</sup> and 14<sup>th</sup> day of treatment. Observed or spontaneously reported side effects (local and systemic) were documented.



**Figure 2a: Grafted ulcer.**



**Figure 2b: Grafted ulcer on follow-up.**

The patients were then subjected to split thickness skin grafting/ flap rotation and the wounds were assessed on fifth post-operative day for skin graft up take and the total no of days of hospitalization were noted (Figure 2a). The follow up of the patients was done at one month after discharge in outpatient department for post skin grafting/ flap complications (Figure 2b).

The results obtained were statistically evaluated and the main parameters which were analyzed were:

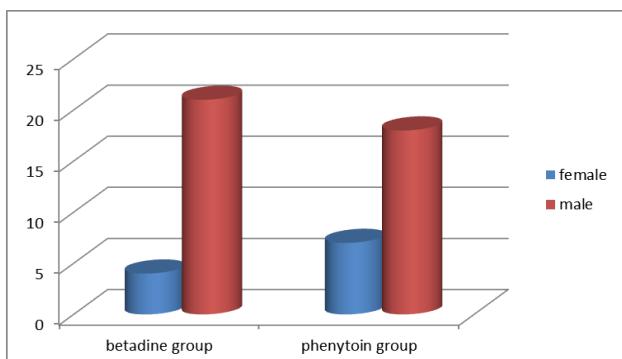
- Rate of granulation tissue formation as percentage of ulcer surface area.
- Graft survival and take up.
- Duration of hospital stay.
- Culture sensitivity.

### Statistical analysis

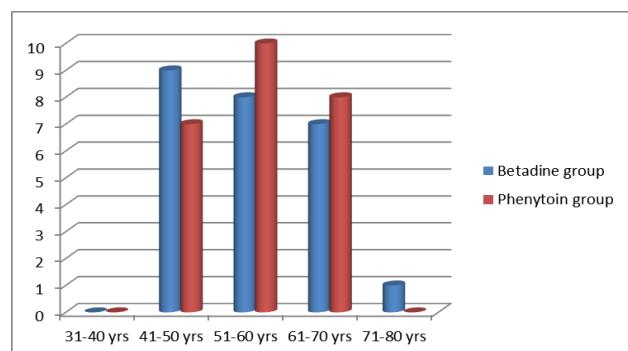
The means were compared using paired and unpaired student's t-test, while number comparisons between the groups for various grading was done using chi-square test and p-value of  $<0.05$  was considered significant. The final data was represented in the form of tables and graphs.

### RESULTS

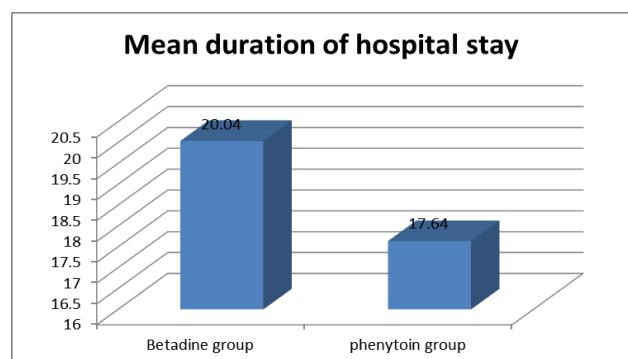
A total of 50 patients were selected for the study. They were divided into groups as aforementioned. The gender wise and age wise distribution of the patients has been described in Figure 3 and 4. The ulcer surface area on day 0 and day 14 in the two groups has been compared in Tables 1 and 2. The rate of granulation tissue formation on days 0 and 14 of both the groups has been compared in Tables 3 and 4. This rate was significantly higher in patients who were treated with phenytoin dressing. The graft uptake in the two groups was compared and the uptake rate of phenytoin group was found to be significantly higher than betadine group (Table 5). The mean duration hospital stay of the two groups was also contrasted and patients with phenytoin dressing has a shorter mean hospital stay although it was not statistically significant (Figure 5). The rate of negative wound culture after 14 days of treatment was also significantly higher in the patients treated with phenytoin dressings (Figure 6).



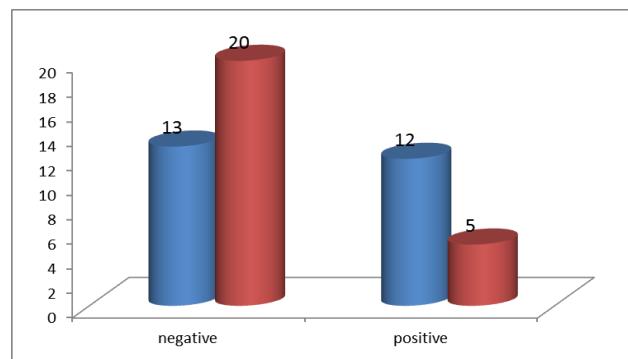
**Figure 3: Comparison of sex wise distribution.**



**Figure 4: Comparison of age wise distribution.**



**Figure 5: Comparison of mean duration of hospital stay.**



**Figure 6: Comparison of culture sensitivity at the end of 14<sup>th</sup> day.**

**Table 1: Ulcer surface area (at day 0).**

Ulcer surface area	Betadine group (n=25) (Mean $\pm$ SD)	Phenytoin group (n=25) (Mean $\pm$ SD)	't' value	p-value
Ulcer surface area	35.70 $\pm$ 5.17	41.14 $\pm$ 4.33	4.030, df=48	0.001*

**Table 2: Ulcer surface area (at day 14).**

Ulcer surface area	Betadine group (n=25) (Mean $\pm$ SD)	Phenytoin group (n=25) (Mean $\pm$ SD)	't' value	p-value
Ulcer surface area	32.43 $\pm$ 5.28 (21)	36.89 $\pm$ 3.77 (20)	3.101, df=39	0.004*

**Table 3: Rate of granulation tissue formation as percentage of ulcer surface area (day 0).**

Parameter	Betadine group, (n=25) (Mean±SD)	Phenytoin group, (n=25) (Mean±SD)	't' value	p-value
Granulation tissue	33.27±5.73	38.87±4.19	3.940, df=48	0.001*

**Table 4: Rate of granulation tissue formation as percentage of ulcer surface area (day 14).**

Parameter	Betadine group, (n=25) (Mean±SD)	Phenytoin group, (n=25) (Mean±SD)	't' value	p-value
Granulation tissue	36.68±5.89 (21)	42.50±4.48 (20)	3.547, df=39	0.001*

**Table 5: Graft take up as percentage of ulcer surface area.**

Parameter	Betadine group, (n=25) (Mean±SD)	Phenytoin group, (n=25) (Mean±SD)	't' value	p value
Graft take up	34.41±5.27	40.57±5.14	4.19, df=48	0.001*

## DISCUSSION

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates and controlling local infections by local medications to the level of providing adequate environment promoting wound healing. This has been achieved by modern wound dressing equines promoting granulation tissue formation.

In a study Tauro et al showed that the mean rate of granulation tissue formation was 87.94%, mean graft take up was 92.31% and mean hospital stay was 32.26 days with negative culture sensitivity was 70%. The control group showed, the mean rate of granulation tissue formation was 74.64%, the mean graft take was 86.15% of total ulcer surface area and mean hospital stay was 54 days with negative culture sensitivity was 54%.<sup>5</sup> In another study, Jayalal et al showed 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 at the end of 14 days and 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.<sup>6</sup>

Reddy et al conducted a study on topical phenytoin in diabetic foot ulcer. Fifty patients were treated with topical phenytoin, and 50 patients matched for age, sex, and ulcer areas, depth, chronicity, and infection were dressed with dry sterile occlusive dressing. They found that both groups improved, but the ulcers treated with topical phenytoin healed more rapidly. Mean time to complete healing was 21 days with phenytoin and 45 days with control. The differences seen were statistically significant ( $P<0.05$ ) via the 2 test. They concluded that phenytoin appears to be useful as a topical agent in promoting the healing of diabetic foot ulcers.<sup>7</sup>

Pandian et al in their study proposed that topical phenytoin was known to trigger granulation tissue and thus accelerating the wound healing on an average of 24 days.<sup>8</sup> In their study 20 patients were subjected to phenytoin dressing out of which 13 patients showed good wound healing effect (65%), 5 patients showed moderate wound healing effect (25%) and 2 patients showed poor wound healing effect (10%).<sup>8</sup> The authors in this study concluded that the treatment of diabetic foot ulcer with topical phenytoin is very cost effective and safe. The topical phenytoin shows accelerated wound healing thereby decreasing the hospital stay of the patient and reduces the expenditure in health care.<sup>8</sup>

In present study, the mean rate of granulation tissue is 42.50%, mean graft take up is 40.57%, mean duration of hospital stay is 17.64 days with negative culture sensitivity 96%. The control group shows mean rate of granulation tissue formation 36.68%, mean graft take up 34.41%, mean duration of hospital stay 20.04 days with negative culture sensitivity of 52%. Common side effects on long term use of phenytoin like coarsening of the faces, enlargement of lips and thickening of face and various hypersensitivity reactions like fever, rash and lymphadenopathy are not seen in our study. The majority of results in present study are in conjunction with previous study although we have a lesser rate of complications as compared to previous such studies.

### Limitations

The most important limitation of the present study is its sample size. A randomized controlled comparative study with a much larger population may help to further substantiate the findings or reveal variations which were not observed in the present study. The cost burden on the patient is also not analysed in this study as it can be influenced by various factors other than the cost of dressings. Phenyltoin dressing was found to be less

expensive compared to conventional moist dressing. However, no commercial preparation of phenytoin dressing is available in the market so far. The quantitative assessment of the post-operative parameters like wound contracture, pain and residual raw ulcer area was also not included in the present study, which if included, might have given a much better analysis of the efficacy of topical phenytoin moist dressing as compared to conventional moist dressing.

## CONCLUSION

Topical phenytoin by decreasing bacterial load, forming healthy granulation tissue helps in better graft take up than the conventional dressing. Due of enhanced healing the overall hospital stay and post-operative complications were less in topical phenytoin dressing group. Thus, topical phenytoin moist wound dressing can be considered as superior option in management of diabetic ulcers. Further studies with larger population will be needed in the future before topical phenytoin dressing can be added to the wide spectrum of treatment modalities available in the management of diabetic ulcers and ulcers of other etiologies.

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*Ethical approval: The study was approved by the institutional ethics committee*

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