# **Original Research Article**

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# Topical phenytoin dressing versus conventional dressing in diabetic ulcers

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#### **ABSTRACT**

**Background:** Diabetic foot ulcer is estimated to affect 15% of all diabetic individuals during their lifetime. Management requires a multisystem approach. Various techniques have been tried to treat chronic ulcers, but none was proved to be ideal.

**Methods:** This is a prospective randomised comparative study, where 56 patients with diabetic foot ulcers admitted in dept of surgery SSG hospital, Baroda, india were divided into two comparable groups. Of which 28 underwent topical phenytoin dressings, remaining 28 underwent Betadine dressing (5% w/v povidone – iodine solution). The variables were compared after 14 days based on rate of granulation tissue formation as percentage of ulcer surface area, wound culture-sensitivity and duration of hospital stay. Chi square test was used to compare the data at each of the assessment point in both groups.

**Results:** In Phenytoin group, the mean rate of healthy granulation tissue formation was 60.71%, and mean hospital stay was 23.96 days with negative culture sensitivity was 54%. The Betadine group showed, the mean rate of granulation tissue formation was 11%, and mean hospital stay was 35 days with negative culture sensitivity was 18%. **Conclusions:** Topical phenytoin dressing considered as superior and cost effective in management of diabetic ulcers.

Keywords: Betadine, Diabetic ulcer, Topical phenytoin

#### INTRODUCTION

Phenytoin as local dressing has been used by many workers because of its positive effects in ulcer healing, such as increase in the proliferation of fibroblasts and deposition of collagen, neovascularization, enhanced granulation tissue formation, decrease in the action of collagenase and bacterial contamination.  $^{1-5}$  and phenytoin increases gene expression of the platelet derived growth factor  $\beta$  chain in macrophage and monocytes. The antibacterial activity of phenytoin contributed to removal of Staphylococcus aureus, *Escherichia coli, Klebsiella species, Pseudomonas*.  $^{6-9}$ 

Since some authors have reported use of phenytoin in healing of different ulcers including diabetic ulcer, it prompted us to conduct a study on the local use of phenytoin on diabetic ulcer healing.

## **METHODS**

Patients admitted in Department of Surgery in SSG Hospital, Baroda, Gujarat, India for Grade I and II diabetic foot ulcers from September to March 2016 were included in the study. Informed consents were taken from all the participants. Institutional ethical committee approved the study design. 56 patients with Grade I and II foot ulcers according to Wagner's wound classification with control of diabetes by oral hypoglycaemic agents or insulin based on fasting blood sugar of 110-130 mg/dl were included and were randomly divided into two equal groups. <sup>10</sup> Patients with Grade III, IV and V foot ulcers

were excluded from study. Details of cases were recorded, including history and clinical examination with baseline characteristics such as general, physical and peripheral vascular state, neurological and neuropathic changes in the lower extremities and ophthalmological examinations. Routine haematology and biochemical investigations, microscopy on urine samples and ulcer swabs for culture and sensitivity etc. Routine preoperative investigations were done in both the groups.

In each patient, 1 ulcer was chosen and surgical debridment was performed when necessary. After slough removal, the surface area was measured, tracing the outline. This outline was transferred to graph paper. On each occasion ulcer areas were measured twice. When identical, the readings were recorded. If not the average was recorded. A good glycemic control was obtained using regular insulin (Hb A1C levels will not be assessed). Wound cultures were obtained using sterile culture swab on the day of initiation of treatment and on 14th day of treatment.

A single 100 mg phenytoin sodium tablet was placed in 5 ml of sterile normal saline to form a suspension. Sterile gauze was soaked in the suspension and placed over the wound. The quantity of powder dusted was depend on the surface area. Dosage used was for 0-5 cm²/100 mg, 5.1-9 cm²/150 mg, 9.1-15 cm²/200 mg, >15 cm²/300 mg respectively.

Conventional Dressing was done with 5% w/v povidone – iodine solution. In both groups before applying the dressing, the wound was cleaned with normal saline. At the end of 14 days the wounds in both the groups were inspected and compared based on the Rate of granulation tissue formation as percentage of the ulcer surface Area, Quality of ulcer bed, Present dimensions and surface area of the ulcer, Wound culture and sensitivity

### **RESULTS**

The 56 patients admitted for the study were divided into two equal and comparable groups. Patients subjected to topical phenytoin dressings were classified under study and those who underwent conventional Betadine dressing were classified as control. Chi square test was used to compare the data for several variables at each of the assessment point in the Phenytoin and Betadine groups.

All patients belonged to middle and low socio economic groups. There were 24 males and 4 females in the study group and 23 males and 5 females in the control group. The age of the patients was varied from 25 to 75 years. Maximum number of cases (52%) belong to the age group of 45 to 65 years. The mean age in study group was 51.35±12.50 years and in control group was 53.17±12.60 years. Among 28 cases in phenytoin group, majority of wounds had surface areas of more than 15cm2 with 16 cases (58%), followed by 7 cases (25%) with 9.1-15cm<sup>2</sup>. Among 28 cases in control group,

majority of the wounds had surface areas of 9.1 to 15 cm<sup>2</sup> with 11 cases (38%), followed by 9 cases (32%) with more than 15 cm<sup>2</sup>.

On comparing the wound site in each group it was found that dorsum of foot was commonest in phenytoin groups with 12 cases (43%) and next commonest was heel, with 8 cases (29%). In control group, the commonest site was dorsum of foot with 10 cases (36%) and next commonest was fore foot with 9 cases (32%).

Among phenytoin group, discharge from wound reduced significantly by day 14 and was seen in only 6 cases (21%), whereas in control group, discharge from wound continued to be present in 23 cases (82%). The result was comparable to study by Vijaya Patil et al which was that wound discharge was reduced significantly in phenytoin dressing. It was observed that the slough from the wound reduced significantly by day 14 and that it was present in only 6 cases (21%), among phenytoin group, whereas in conventional group, slough continued to be present in 23 cases (82%). This difference was found to be statistically Significant. Status of wounds before and after phenytoin dressing is shown in (Figure 1 and 2).



Figure 1: Ulcer before phenytoin dressing.



Figure 2: Ulcer after phenytoin dressing.

Comparison of Granulation Tissue among cases and controls were done at day 14. This difference was found to be statistically significant (Table 1).

The microbiological evaluation of the wounds in both phenytoin and control groups revealed that Staphylococcus aureus was commonest organism. The other organisms isolated from both cases and controls have been shown in the Table 2.

Patients in both groups were assessed for the effect of topical phenytoin agents on the bacterial load as percentage of people who are culture sensitivity negative at the end of 14 days (Table 3). In both groups, no complications occurred during the application of dressings. The quality of life of the patient in both the groups was assessed by the assessment of total hospital stay as number of days of admission in the hospital. The mean hospital stay in control group was 35.10±14.23 (SD) days and that in the study group was 23.96±10.61 (SD) days. P value is <0.0016 which is highly significant.

Table 1: Comparison of granulation tissue among cases and controls at day 14.

Day 14	Betadine	Phenytoin
Pale	23	8 (28%)
Normal granulation tissue	3	17 (62%)
Granulation tissue absent	2	3 (12%)

Table 2: Organisms isolated from wound.

Organisms	Cases	Control
Streptococcus	1	1
Proteus	1	1
Klebsiella	1	1
Citrobacter	1	2
Pseudomonas	3	4
E.coli	5	3
Staphylococcus aureus	15	14
Sterile	1	2

Table 3: Negative culture sensitivity at the end of 14 day.

Culture sensitivity	Betadine	Percentage (%)	Phenytoin	Percentage (%)
Positive	23	82	13	46
Negative	5	18	15	54



Figure 3: Ulcer before phenytoin dressing.



Figure 4: Ulcer after phenytoin dressing.

In this era of globalization, the cost of treatment of chronic conditions has a key role to play and chronic wound management and its financial impacts are very important for a surgeon. The cost effectiveness of topical phenytoin over conventional dressing techniques is believed to be due to,

- Lesser time required for wound to heal or granulate
- Better response to defenitive treatment modalities like graftings, flaps etc. After removal of topical therapy
- Low cost of the phenytoin, compared to conventional dressing material.

#### **DISCUSSION**

Phenytoin has been investigated as a treatment for more than 100 diseases. A frequent observed and unwanted side effect of phenytoin, an anticonvulsant medication, is gingival hyperplasia, especially in children Bethedsa. <sup>13</sup> This side effect suggested that phenytoin can induce the growth of connective tissue, and may have the ability to promote wound healing. This stimulated the first controlled clinical trial in 1958, which found that the periodontal patients with surgical wounds who were pretreated with oral phenytoin had less inflammation, less pain, and accelerated healing when compared with controls Shapiro. <sup>14</sup> Phenytoin has been investigated to

treat ulcers in epidermolysis bullosa and other inflammatory conditions. The prospective, controlled trial by Muthukumarswamy et al examined the use of topical phenytoin versus control therapy in 100 diabetic ulcer patients. 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, and then dry dressing applied daily. Mean healing time was 21 days in the phenytoin group compared to 45 days in the control group (p<0.05%). A study conducted by Pai et al showed good granulation tissue with topical phenytoin. Comparison of the present study to study by Muthukumarswamy et al (M.K.M.G. et al) was done (Table 6).

Table 4: Comparison of the present study to study by Muthukumarswamy et al.

	Muthukumara Swamy et al		Present study	
	Phenytoin (N=50)	Betadine (N=50)	Phenytoin (N=28)	Betadine (N=28)
Mean age in years	56.4	58.7	51.35	53.17
Rate of healthy granulation tissue at 14 day	46%	20%	60.71%	11%
Hospital stay in days	21	45	23.96	35
Negative bacterial culture	82%	54%	54%	18%

In study conducted Vijaya Patil et al DM was more common among male (74%) as compare to female with mean age in study group was 48.5±12.49 years and in control group was 49.74±10.9 years. They took 100 patients which were divided equally in both groups. Rate of healthy granulation at 14 days was 62% in study group and 12% in control group. Hospital stay in study group was 20.04±9.14 days and in control group it was 26.10±5.70 days.

Another study conducted by Tauro L.F et al who took 200 patients which was equally divided in both group. <sup>16</sup> The mean age of study group was 50.11±14 years and in control group was51.41±13.4 years. In the study group, 65 patients were males and 35 were females. In the control group, males were 67 and females were 33 in number. The mean rate of granulation tissue formation at the end of 14 days in the study group was 87.94% and in control group 74.64%.70% of the study group showed negative culture sensitivity at the end of 14 days, whereas in control group it was 54%. The total hospital stay in study group was 36.26±2.64 days and in control group was 40.97±3.31 days.

In present study, total 58 patients were taken which was equally divided in both group. Both study and control groups, diabetes was more common among male (84%) as compare to female. The mean age in study group was 51.35±12.50 years and in control group was 53.17±12.60 years. Which was comparable to all 3 studies. 54% of the study group showed negative culture sensitivity at the end of 14 days whereas in control group it was 18%. While in study done by Tauro LF et al, negative culture sensitivity at the end of 14 day, 70% in study group and 54% in control group. <sup>16</sup> Topical phenytoin used in wound therapy appears to be well tolerated. Its adverse effects are mild and infrequent. In this study, no complications occurred during the application of dressings. A generalized rash

that resolved when treatment was stopped has also been reported Rhodes et al. 11 Hypertrophic granulation tissue was noted in 10~36 percent of patients in two studies Muthukumaraswamy et al; Pendse et al. 9 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. Only one case report showed significant levels of serum phenytoin after topical phenytoin Anstead et al. 17

#### **CONCLUSION**

In the present study, it was concluded that topical phenytoin dressing is better by forming healthy granulation tissue earlier and decreasing bacterial load and because of enhanced healing, reduced overall hospital stay. Thus, topical phenytoin moist wound dressing can be considered as superior and cost effective option in management of diabetic ulcers. But further studies with larger population will be needed 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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institutional ethics committee

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