A Study of Efficacy of Topical Phenytoin in the Management of Diabetic Ulcer

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Abstract

Background: Diabetic ulcer is the most frequent reason for hospitalization in patients with diabetes. It has increased the cost of treatment and hospitalization of these patients. Currently a lot of attention is being placed on the development of expensive topical growth factors for wound healing. Thus there remains a quest for better wound healing agents. One such agent is phenytoin which is cheap, easy to use and readily available for medical practice. Phenytoin (diphenylhydantoin) was initially introduced into therapy for the effective control of convulsive disorders. A common side effect with systemic phenytoin treatment is the development of fibrous overgrowth of gingiva. This apparent stimulatory effect of phenytoin on connective tissue suggested an encouraging possibility for its use in wound healing. To study the efficacy of topical phenytoin dressing over conventional dressing in the management of diabetic ulcers, in terms of days required for healing, rate of granulation tissue formation, quality of graft bed, graft uptake, effect on bacterial growth and side effects of topical phenytoin.

Method: All patients undergo detailed clinical examination and relevant investigations and the wounds are thoroughly debrided. The surface area is measured tracing the outline on transparent paper. This outline is transferred to a graph paper for area measurement. The patients are followed up on a daily basis for 14 days in both study and control groups. The control group and study group are subjected to twice-daily dressing. Both the groups are first cleaned with normal saline and 5% povidone iodine. The study group is then subjected to topical phenytoin dressing. Sterile gauze is soaked in preparation of i.v. phenytoin and placed over the wound. Once these parameters are assessed, both the groups subjected to split thickness skin grafting. Both groups are given the same systemic antibiotics during the postoperative period. Both the groups were compared in terms of discharge, slough, wound area reduction and duration of hospital stay.

Results: This study has shown better granulation tissue formation, graft uptake, negative bacterial growth and decreased hospital stay in patients receiving phenytoin dressing than patients receiving betadine dressing. There were no side effects in patients with phenytoin dressing.

Conclusion: Phenytoin is a cheap, readily available and easy to use alternative in the treatment of diabetic ulcers.

Keywords: Diabetic ulcers, phenytoin dressing, betadine dressing, granulation tissue, graft uptake, graft bed, bacterial growth, hospital stay, phenytoin side effects.

Date of Submission: 01-08-2017
Date of acceptance: 23-08-2017

I. Introduction

Diabetes mellitus comprise a group of common metabolic disorder that share the phenotype of hyperglycaemia. In this millennium where mankind has succeeded in deciphering the human genetic code, the issue of chronic wound management still remains an enigmatic challenge. Chronic wounds, especially non healing types, are one of the most common surgical conditions a surgeon comes across. From time immemorial Doctors have been trying many methods to treat these types of wounds. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that imposes a tremendous burden on individual.
The peculiarity of a chronic wound is that, whatever management you give, they refuse to heal, especially pressure ulcers or bed sores. The notion that wounds should be kept dry, although still held by a considerable number of clinicians, is steadily losing ground. We now know that wounds re-epithelial much faster or develop granulation tissue faster when treated with dressings which allow moist wound healing. We recognize that occluding wounds does not lead to infection. Even though many modalities of wound care have come up to assist a surgeon, example the use of compression bandages to treat venous ulcers, the problem of chronic wound still remains.

A wound care revolution is currently in the making. Many techniques have been tried over the centuries to heal chronic leg ulcers. Although wound dressing have been used for at least two millennia, there exist no ideal dressing. Surgical dressing of both open and closed wound is based mainly on tradition, training and surgeons own philosophy. During the last two decades a wide variety of innovative dressings have been introduced.

Neuropathy presents in many forms including focal neuropathy and polyneuropathy and autonomous neuropathy. Patient with distal sensory neuropathy are predisposed to develop Charcot’s joint which may mimic gout or degenerative joints. Treatment involves surgical debridement and antibiotic treatment. Diabetic neuropathy has been defined as peripheral nerve dysfunction after exclusion of other causes which may range from hereditary, traumatic, compressive, metabolic, toxic, nutritional infectious, immune mediated neoplastic and any other secondary systemic illness.

**Classification Of Diabetic Neuropathy**

A) Diffuse
i. Distal semetric sensory motor polyneuropathy
2. Autonomic neuropathy

A. submotor
B. cardiovascular C. gastrointestinal D. genitourinary
3. Symmetric proximal lower limb motor neuropathy. B) Focal
i. Cranial neuropathy
2. Radiculopathy
3. Entrapment neuropathy
4. Asymmetric lower limb motor neuropathy.

Non healing chronic ulcers are regularly encountered by a surgeon. The peculiarity of a these wounds are that inspite 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 these wound is a constant challenge for the surgeon. The notion that wounds should be kept dry, although still held by a considerable number of surgeon, is steadily losing ground. We now know that wounds develop granulation tissue when treated with dressing which allow moist wound healing. People have tried various non-conventional topical therapies in wound healing, such as aloe vera, collagen, gentian violet, benzoyl peroxide, impregnated guaze, insulin, mercurochrome, oxygen therapy, sugar and vinegar. Studies prove that topical phenytoin promotes healing of decubitus ulcer, pressure ulcer & leprosy ulcer and was found to be of superior. This study was conducted to assess efficacy of topical phenytoin as compared to conventional dressing in diabetic ulcers, also to assess the percentage of graft uptake of phenytoin treated wounds and to document any local or systemic side effects of topical phenytoin applications.

**II. Aim And Objectives Of The Study**

To study the efficacy of topical phenytoin over conventional dressings in the management of diabetic ulcers,
- No of days required for healing
- Days required for granulation tissue formation (rate)
- Quality of graft bed & skin graft take
- Effect on bacterial load
- Side effects of topical phenytoin dressing
III. Materials And Methods

This prospective randomized comparative study included 100 patients with diabetic ulcers admitted in Madurai Medical College, Madurai from July 2016 to June 2017 satisfying all the inclusion criteria mentioned below after the clearance from the ethical committee was obtained. The main inclusion criteria were

- grade I and II foot ulcers according to Meggitt-Wagner clinical classification
- control of diabetes mellitus with oral hypoglycemic agents or insulin

The main exclusion criteria for the study were

- grade III, IV, V foot ulcers according to Meggitt-Wagner clinical classification chronic ulcer of other etiology
- other co-morbid conditions like renal failure, generalized debility which adversely affect wound healing
- Patients with allergy to phenytoin

The sample population divided into two equal and comparable groups based on willingness to undergo topical phenytoin therapy for the wound. Those not willing were subjected to conventional wound care forming the control group. Selection of patients was done by purposive sampling method. 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. The wounds were thoroughly debrided. After slough removal, the surface area was measured, tracing the outline on butter paper. This outline was transferred to a graph paper. On each occasion ulcer areas were measured twice. The average was recorded.

Sterile gauze is soaked in preparation of i.v. phenytoin and placed over the wound at 20mg/cm2 TBSA. Conventional dressing was done with 5%w/v povidone-iodine solution. Dressings were done on twice daily basis. The patients were followed up on a daily basis for 4 days in both study and control groups. Wound culture was obtained at the start of the treatment and on the 4th day of treatment. At the end of 4 days the wounds in both the groups were inspected and compared based on the following parameters

- rate of granulation tissue formation as percentage of ulcer surface area
- quality of ulcer bed
- present dimensions and surface area of ulcer

Observed or spontaneously reported side effects (local and systemic) were documented. The patients were then subjected to split thickness skin grafting. Both the groups were given the same systemic antibiotics during the post operative period. The wounds were assessed on fifth post operative day for skin graft take and the total number of days of hospitalization was noted. The follow up of the patients was done at one month after discharge in outpatient department to assess wound dimensions and post skin grafting complications. The results obtained were statistically evaluated and the main parameters which were analysed were

- rate of granulation tissue formation as percentage of ulcer surface area
- graft survival and take up
- duration of hospital stay

The variables were compared using Paired and Unpaired Student's t-test and P value of <0.05 was considered significant.

IV. Observation And Results

The 100 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 moist wound dressing were classified as control.

| Table 1: Age wise distribution of patients. |
|-----------------|--------|--------|--------|--------|--------|
| Age Group (yrs) | 31-40  | 41-50  | 51-60  | 61-70  | 71-80  |
| Betadine        | 1      | 14     | 20     | 12     | 3      |
| Phenytoin       | 6      | 10     | 21     | 9      | 4      |
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Mean age of Betadine group is 56.12 ± 8.76
Mean age of Phenytoin group is 54.54 ± 11.003
P value 0.429 Not significant

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<tr>
<th>Table 2: Ulcer surface area</th>
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<tr>
<td>Group</td>
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<tr>
<td>ULCER AREA</td>
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<tr>
<td>Betadine</td>
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<tr>
<td>Phenytoin</td>
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<th>Table 3: Rate of granulation tissue formation as percentage of ulcer surface area.</th>
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<td>Group</td>
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<td>Betadine</td>
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<tr>
<td>Phenytoin</td>
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<th>Table 4: Graft take up as percentage of ulcer surface area.</th>
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<td>Group</td>
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<td>STSG</td>
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<td>Betadine</td>
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<td>Phenytoin</td>
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Assessment of graft take up was done at the end of the 5th post operative day as the percentage of ulcer surface area is given above.
The mean graft take up in the study group is 37.35% ± 5.64(SD) and in the control group is 40.37% ± 2.83(SD).

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<th>Table 5: Duration of hospital stay.</th>
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<td>Group</td>
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<tr>
<td>DAYS</td>
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<tr>
<td>Betadine</td>
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<td>Phenytoin</td>
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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 31.8 ± 4.63(SD) days and that in the study group was 27.48 ± 2.68 (SD) days. P value is <0.001 which is highly significant

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<th>Table 6: Percentage of negative culture sensitivity at the end of 14 days.</th>
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<td>Group</td>
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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 4 days. 90% of the study group showed negative culture sensitivity at the end of 4 days whereas in control group it was 74%. In both groups, no complications occurred during the application of dressings, skin grafting or in the post operative period. The patients were followed up after one month of discharge.

The main post operative parameters noted in both the groups:
- wound size
- contracture
- pum
- infection

All these parameters were less in study as compared to control.

V. Analysis Of Data

Both groups had comparable age and sex distribution as seen in above depicted graphs. The mean rate of granulation tissue formation in study group is 95.93cm$^2$ of total ulcer surface area and in control group is 98.09 cm$^2$. The results were analysed by unpaired student t-test which showed highly significant difference in rate of granulation tissue formation (p<0.0002). The mean graft take up in the study group is 99.03cm$^2$ and in the control group is 97.61cm. The results were analysed by unpaired student t-test which showed highly significant difference in graft take up (p of 0.001). The total number of days of hospital stay for the patient was also compared. The mean number of days of hospital stay in control group was 31.3 days and that in the study group was 27.8 days. The results were analysed by unpaired student t-test which showed highly significant difference in the number of days of hospital stay (p<0.0002). 45% of the study group showed negative culture sensitivity at the end of 4 days whereas in control group it was 37%.

VI. Discussion

This study was done as a prospective randomized controlled comparative study to compare the efficacy of topical phenytoin dressing to conventional wound dressing in the management of diabetic ulcer.

Table 7: Comparision of present study to study by Muthu kumaraswamy et al shows following similarities.

<table>
<thead>
<tr>
<th>Muthukumara Swamy et al Present Study</th>
<th>Phenyo in 56.4</th>
<th>Betadine 58.7</th>
<th>Phenyo in 54.54</th>
<th>Betadine 56.12</th>
</tr>
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<tr>
<td>Mean age in Years</td>
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<tr>
<td>Graft uptake in Percentage</td>
<td>72.4%</td>
<td>58.4%</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>Hospital stay in Days</td>
<td>21</td>
<td>45</td>
<td>27</td>
<td>32</td>
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<tr>
<td>Negative culture bacterial</td>
<td>82%</td>
<td>54%</td>
<td>92%</td>
<td>70%</td>
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DOI: 10.9790/0853-1608070511  www.iosrjournals.org  9 | Page
Mean age group in Muthu kumaraswamy et al study in study group is 56.4 yrs and in the control group is 58.7yr while in the present study it is 54.54yrs in study group and 56.12yrs in control group. The percentage of graft take up in Muthu kumaraswamy et al study in the study group is 72.4% and in the control group is 58.4% while the percentage of graft take up in the study group is 84% and in the control group is 74% The duration of hospital stay in Muthu kumaraswamy et al study in control group was 45days and that in the study group was 21 days while in the present study the mean hospital stay in control group was 32days and that in the study group was 27days. The negative wound culture sensitivity at the end of 14days in Muthu kumaraswamy et al study was 82% in study group and 54% in control group. Whereas in the present study the negative culture sensitivity at the end of 14days was 92% of the study group and in control group it was 70%.

Important difference between present study and Muthu kumaraswamy et al study in that in the latter a thin layer of phenytoin powder is laid over the wound and covered with a dry gauge as the method of application.

**VII. Limitations Of The Study**

The most important limitation of the present study is its sample size. A randomised controlled comparative study with a much larger population may help to further substantiate the findings of this 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. Phenytoin dressing was found to be less expensive compared to conventional moist dressing. However, no commercial preparation of phenytoin is available in the market so far.

**Summary**

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.
- Considerable effect on bacterial load was seen in topical phenytoin group when compared to conventional group.
- Shorter duration of hospital stay was seen in topical phenytoin group when compared to conventional group.
- Topical phenytoin dressing thus is an effective, inexpensive and widely available therapeutic agent in wound healing.
- Follow up observations revealed that topical phenytoin dressing group suffered lesser post skin grafting complications like wound contracture, residual raw area and pain compared to conventional group.

**VIII. Conclusion**

In the present study it was concluded that topical phenytoin by decreasing bacterial load, forming healthy granulation tissue helps in better graft take up than the conventional dressing. Because of enhanced healing and overall hospital stay, the 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. But 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.

**References**


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