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Role of topical phenytoin (Diphenylhydantoin) dressing in diabetic ulcers: A comparative study with conventional dressing

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Abstract
Introduction: The stimulatory effect of phenytoin on connective tissue suggested possibility for its use in wound healing. Oral phenytoin was first introduced as an antiseizure medication in 1937. Over 60 years investigators have shown an interest in how topical phenytoin may be used to promote wound healing in a variety of chronic wounds.
Materials and Methods: A sample of 40 patients with diabetic ulcers was selected using purposive sampling technique. The patients were divided into two groups: Group A (Phenytoin group) (n=20) and Group B (conventional group) (n=20). In Group A, the patient's dressing were done using phenytoin and in Group B, with povidine. The patients were followed up on a daily basis for 9 days in both study and control groups. Wound culture was obtained at the start of the treatment and on the 7th day of treatment. Then the patients were subjected to split thickness skin grafting on 10th day. The follow up of the patients were done at one month after discharge in outpatient department for post skin grafting complications.
Result: The mean duration of hospital stay in phenytoin group was 21.35±4.71 (SD) days and that in the conventional group was 27.3±6.48 (SD) days. One month follow up complications in conventional group were more as compared to phenytoin group.
Conclusion: Topical phenytoin dressing helps in better granulation tissue formation and better graft take up than the conventional dressing. Hospital stay and post-operative complications were less in topical phenytoin dressing group as compared to conventional dressing group.
Conflict of interest: Nil
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Keywords: Diabetic ulcer, Phenytoin, Diphenylhydantoin

Introduction
Diabetic ulcer is a common complication in patients with diabetes and is a major cause of morbidity and increased hospital care cost for the patients. Though there are many modalities of wound care, the problem of treating diabetic wounds is still enormous. Prevalence of diabetic foot ulcer in clinical population is 3.61% and it is estimated that ulcer occurs in 15% of all diabetic individuals during their lifetime. Diabetic foot ulcers precede almost 85% of amputations in India [1]. Management of the diabetic foot requires a multisystem approach, which includes the nervous, vascular, skeletal, immune, and integumentary systems [2].
The pathophysiological changes in multiple organ systems are the result of metabolic deregulation associated with diabetes mellitus which imposes tremendous burden on individual [3].
Currently a lot of attention is being placed on the development of expensive topical molecular factors for wound healing like epidermal growth factors, tissue stimulating factor, vacuum assisted dressing and dressing with hyperbaric oxygen. The efficacy of such agents is still questionable and the cost factor should be kept in mind. 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 [4].

Phenytoin 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 [5-9]. The antibacterial activity of phenytoin contributes to removal of Staphylococcus aureus, Escherichia coli, Klebsiella species, Pseudomonas [10-12] thus improves quality of graft bed and better graft up take. This ensures better wound management for the patient.

Our study has been done to assess the efficacy of topical phenytoin dressing as compared to conventional wound dressing in diabetic ulcers and to know if phenytoin is a better and cheaper alternative option in the management of diabetic ulcers.

Material and methods

We conducted this study to compare the efficacy of topical phenytoin with conventional wound dressings in healing of diabetic ulcers, in terms of:

- Quality of graft bed and skin graft up take.
- Effect on bacterial load.
- Side effects of topical phenytoin dressing.

Total 40 patients (20 in each group) were admitted in surgical wards of Government Medical College and Hospital, Patiala were included in study.

Patients with diabetic ulcer reported to orthopedic and surgery department of Government Medical College, Patiala from 2014 to 2017. A sample of 40 patients was selected using purposive sampling technique. The patients were divided into two groups: Group A (Phenytoin group) (n=20) and Group B (conventional group) (n=20). In Group A, the patient's dressings were done with phenytoin and in Group B, with povidine iodine 5% w/v solution. 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. After satisfying the inclusion and exclusion criteria, the selected patients were randomly assigned into treatment group A (phenytoin group) and group B (conventional group). In each patient one ulcer was chosen and surgical debridement was done when necessary. 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 surface area was measured twice. When identical, the reading was recorded. If not, the average was recorded and surface area calculated by multiplying the maximum perpendicular length by the maximum width of the wound bed by ruler after tracing the wound on graph paper and typically recorded in cm^2 by Flanagan method.

One 100 mg 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 appox. $20mg/cm^2$ SA. Conventional dressing was done with 5% w/v povidone-iodine solution. Dressings were done on daily basis in both phenytoin and conventional groups. The patients were followed up on a daily basis for 9 days in both study and control groups. Wound culture were obtained at the start of the treatment and on the 7^{th} day of treatment. The patients were observed for spontaneously reported side effects (local and systemic) and documented. Efficacy of dressing was assessed by granulation tissue at day before surgery and at day 9 as granulation tissue percentage which was measured by using the formula [10] is: (wound size-the wound size that without granulation coverage)/ wound size×100%

Then the patients were subjected to split thickness skin grafting on 10^{th} day and the wounds assessed on fifth post-operative day for skin graft up take and the total number of days of hospitalization also recorded. The follow up of the patients was done at one month after discharge in outpatient department for any post skin grafting complications.

Diabetic Foot Ulcer [Meggit- 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

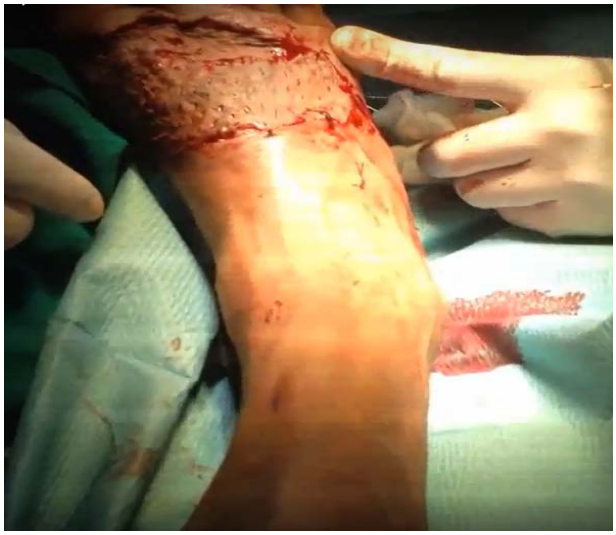
Inclusion Criteria

- Grade I and II foot ulcers according to Meggit-Wagner clinical classification
- Control of 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
- Other co-morbid conditions like renal failure, generalized debility which adversely affect wound healing
- Patients with allergy to phenytoin.

Image



Split Thickness Skin Graft

Results

The efficacy of the dressing or quality of graft bed was assessed as the percentage of ulcer surface area covered by granulation tissue at 9^{th}day. In our study mean percentage of granulation tissue was calculated on day 9, we found that in phenytoin dressing group it was 84.36±10.53 (SD) while in conventional group it was 74.93±12.0 (SD).

Graft uptake assessed at the end of 5^{th} post-operative day in the phenytoin group was 89.05±11.30(SD) and in the conventional group was 76.63±11.73(SD).

Table 1: Graft Uptake Percentage on 5th Post-Operative Day

Group	Frequency	Mean±SD (Graft up take % age)	t-test	p value	Sig.
Phenytoin	20	89.05±11.30	3.408	0.002	Significant
Conventional	20	76.63±11.73			

We found that percentage of pus culture which become negative on day 7 was 45% in phenytoin group and 20% in conventional group. Our study shows that phenytoin group decreases bacterial load more as compared to conventional group.

Table 2: Comparison of Pus Culture on Day 1 & Day 7

Pus Culture	Day 1		Day 7		X^2	p value	Sig.
	Frequency	Percentage	Frequency	Percentage			
Phenytoin	18	90%	9	45%	10.730	0.011	Significant
Conventional	18	90%	14	70%	2.956	0.150	Non-Significant

The main post- operative parameters noted in both the groups during follow up were: presence of infection, wound size, hyperpigmentation, contractures and pain. All these parameters were lower in the phenytoin group with 10 % as compared to conventional group with 20%.

Table 3: Follow Up at One Month (Complications)

Complication	Phenytoin		Conventional		X^2	p value	Sig.
	Frequency	Percentage	Frequency	Percentage			
Any Complication	2	10%	4	20%	0.22	0.635	Not Significant

Discussion

Mean age in present study was 53.50±7.52 (SD) yr in phenytoin group, while 53.35±7.29 (SD) yr in conventional group. Almost similar results were seen in studies conducted by Rituraj [11] *et al*. and Jayalal JA [12] *et al*. Rituraj *et al*. found that mean age was 55.71±11.5(SD) in phenytoin group and 54.31±12.24(SD) in conventional group and Jayalal JA [12] *et al*. found that mean age was 52.63± 7.1(SD) in phenytoin group and 53.1±6.8(SD) in conventional group.

Maximum number of cases were present in 51-60 years with 57.5 percentage of the total number of cases. Vardhan A [13] *et al*. also had most cases in 51-60 yr which were 50% cases. Yadwadkar S [14] *et al*. also had most of cases in 51-60 yrs which were 44% of cases. Our results were slightly higher as compared to these studies. Our study showed that 67.5% were male, while 32.5% were female. Almost similar results were found by Tauro LF [15] *et al*. and they found, 66% cases were male while 34% cases were female. Kumar N [16] *et al*. found that 63% were male, while 37% were female. Our study found that diabetic ulcer was more common in males.

Our study found that overall most common organism in diabetic ulcer was staph aureus with 47.5% of the total in both groups. Similar results were seen by the studies conducted by Kodela SR [17] *et al*., they also found that most common microorganism was staph aureus with 45% of the total and Jayalal *et al*. found that staph aureus was the most common organism in 48.33% of the total.

The efficacy of the dressing or quality of graft bed was assessed as the percentage of ulcer surface area covered by granulation tissue at 9thday. In present study mean percentage of granulation tissue was calculated on day 9, we found that in phenytoin it was 84.36±10.53 (SD) while in conventional group it was 74.93±12.0 (SD). Rituraj [11] *et al*. calculated same on day 14 that was 88.21±6.98(SD) in phenytoin group and 71.32±7.9(SD) in conventional group. Similarly Tauro LF [15] *et al*. found that same was 87.94±7.33(SD) in phenytoin group and 74.64±8.04(SD) in conventional group. Our results were comparable to these studies.

The total hospital stay (the total number of days of admission in the hospital) was assessed. The mean hospital stay in the phenytoin group was 21.35±4.17 (SD) days and that in the conventional group was 27.30±6.48 (SD) days. Similar results were found by Mujeeb MMA [18] *et al*., they found that the mean hospital stay in the phenytoin group was 16.26±2.64 (SD) days and that in the control group was 40.97±3.31 (SD) days and Bharadva PB [19] *et al*. that mean hospital stay in the phenytoin group was 23.96 days and that in the control group was 35 days in their respective studies. Our study found that hospital stay in phenytoin group was less than conventional group.

The main post- operative parameters noted in both the groups during follow up were residual infections, wound size, hyperpigmentation, contractures and pain. All these parameters were lower in the phenytoin group with 10 % as compared to conventional group and similar results were seen by the studies conducted by Selvaraj J [20] *et al*. and Azeez A [21] *et al*. in which both found that all these parameters are less in study group than conventional group.

Conclusion

In this study, we concluded that topical phenytoin dressing helps in better granulation tissue formation and better graft take up than the conventional dressing. Because of enhanced healing and antibacterial properties of topical phenytoin, overall hospital stay and post-operative complications were less in topical phenytoin dressing group. Thus, topical phenytoin dressing can be considered as superior option in the management of diabetic ulcers. But further studies with larger sample is 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.

Consent – Consent taken from all the patients as per consent form in written.

Ethical Study – Study is done as per ethics committee of the institute

References

1. Pendse S. Understanding diabetic foot. Int J Diabetes Dev Ctries. 2010; 30:75-79.

2. Laughlin RT, Calhoun JH, Mader JT. The diabetic foot. Am Acad Orthop Surg. 1995; 3:218-25.
3. Harrison's Principle of Internal Medicine: Diabetes Mellitus Vol 2, 16edn, USA; McGraw-Hill, 1999; 21:09-37.
4. Kimball OP, Horan TN. The use of Dilantin in the treatment of epilepsy. Ann Intern Med 1939; 13:787-93.
5. DaCosta ML, Regan MC, al Sader M, Leader M, Bouchier-Hayes D. Diphenylhydantoin sodium promotes early and marked angiogenesis and results in increased collagen deposition and tensile strength in healing wounds. Surgery. 1998; 123:287-93.
6. Kato T, Okahashi N, Kawai S, Kato T, Inaba H, Morisaki I, Amano A. Impaired degradation of matrix collagen in human gingival fibroblasts by the antiepileptic drug phenytoin. J Periodontol. 2005; 76:941-50.
7. Moy LS, Tan EM, Holness R, Uitto J. Phenytoin modulates connective tissue metabolism and cell proliferation in human skin fibroblast cultures. Arch Dermatol. 1985; 121:79-83.
8. Genever PG, Cunliffe WJ, Wood EJ. Influence of the extracellular matrix on fibroblast responsiveness to phenytoin using in vitro wound healing models. Br J Dermatol. 1995; 133:231-5.
9. Swamy SM, Tan P, Zhu YZ, Lu J, Achuth HN, Moochhala S. Role of phenytoin in wound healing: microarray analysis of early transcriptional responses in human dermal fibroblasts. BiochemBiophys Res Commun. 2004; 314:661-6.
10. Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA *et al*. Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. Dia- betes Care 1999; 22:157-62.
11. Rituraj, Aggarwal S, Chatterjee S. Topical phenytoin: role in diabetic ulcer care. International Journal of Interdisciplinary and Multidisciplinary Studies. 2015; 2(6):93-7.
12. Jayalal JA, Kumar SJ, Dhinesh, Thambithurai D, Kader JMA. Efficiency of Topical Phenytoin on Healingin Diabetic Foot Ulcer: A Randomized Controlled Trial. Int J Sci Stud. 2015; 3(3):84-9.
13. Vardhan A, Garg P, Sehgal VK, Naidu DC, Bankar M, Mittal S. Efficacy of topical phenytoin in healing diabetic foot ulcer. Int J Basic Clin Pharmacol. 2016; 5(6):2645-8.
14. Yadwadkar S, Thipse, Mutha S, Dash N, Khalkar A, Gadekar J. Role and Side Effects of Topical Phenytoin Dressing in Diabetic Foot Ulcer as Compared to Conventional Betadine Dressing. JMSCR 2015; 3(12):8781-8.
15. Tauro LF, Shetty P, Dsouza NT, Mohammed S, Sucharitha S. A Comparative Study of Efficacy of Topical Phenytoin vs Conventional Wound Care in Diabetic Ulcers. International Journal of Molecular Medical Science, 2013; 3(8):65-71.
16. Kumar N, Pavan BM, Arava S, Kumar K. A Comparative Study of Topical Phenytoin VS Conventional Wound Care in Diabetic Ulcer. Journal of Dental and Medical Sciences. 2015; 14(4):6-11.
17. Kodela SR, Kumar TJP, Vivek. Out Come of Topical Phenytoin in the Management of Diabetic Ulcers Journal of Dental and Medical Sciences. 2016; 15(7):39-54
18. Mujeeb MMA, Mutha AS. Comparative efficacy and safety of topical phenytoin versus conventional wound care in diabetic ulcer. Journal of Evolution of Research in Medical Pharmacology. 2015; 1(1):16-20.
19. Bharadva PB, Choksi DB, Damor S, Shah J. Topical phenytoin dressing versus conventional dressing in diabetic ulcers. IntSurg J. 2017; 4(5):1682-6.
20. Selvaraj J, Jeevaraman S. Efficiency of Topical Phenytoin on Healing In Diabetic Ulcer: A Randomized Control Trial. J. Evolution Med. Dent. Sci. 2016; 5(23):1225-8.
21. Azeez A, Venkatesh NS, Shivakumar T. Analysis of outcome of diabetic foot ulcer following topical phenytoin and betadine use: a comparative study. IntSurg J. 2017; 4(4):1263-6.