

Efficacy of topical phenytoin in healing diabetic foot ulcer

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ABSTRACT

Background: India is fast becoming world diabetes capital. Complications are a cause of hospitalization in patients with diabetes mellitus especially foot complications. Gauze moistened with saline has been the standard method.

Methods: The study was done from June 2015 to June 2016. The objective of this study was to assess the efficacy of topical phenytoin compared to standard and conventional methods of wound care in improving the healing process. In this randomised control trial, the data from 70 patients with diabetic ulcers was collected, 35 patients underwent topical phenytoin dressing while remaining 35 underwent conventional wound care. Histopathological and Clinical examination were done and the following parameters were calculated: Granulation tissue formation in 2 weeks and Mean duration of hospital stay.

Results: In this study, Mean hospital stay in days was 33.4 in Phenytoin treated group and in other group with use conventional materials, the mean hospital stay in days was 39.7 days. Granulation tissue formation was faster as compared to conventional materials of Dressings.

Conclusions: In this study we conclude Topical phenytoin helps in faster healing of Diabetic Foot Ulcers and it also reduces the mean hospital stay of the patients.

Keywords: Diabetic foot, Standard and conventional normal saline dressing, Topical phenytoin

INTRODUCTION

Diabetes is a disease of modern era and India is marching toward to be the capital of diabetes. India has a lot of diabetic patients. Total world has 7% of the population with diabetes. India followed by China and USA on the top amongst diabetic country list.¹ Diabetic foot syndrome is a most common and preventable complication of diabetes. About 15% of diabetic individual will develop diabetic foot syndrome in their life time.² Diabetic foot ulcer precedes maximum number of amputation in individuals. This can be related to many social and cultural patterns in India such as lack of knowledge and facility for adequate diabetic care,

poverty, and other socioeconomic conditions.³ The optimal topical therapy for DFU remains ill-defined. Gauze moistened with saline has been the standard method; however, it is difficult to maintain a moist wound environment continuously. Subsequently, various wound gels, growth factors, enzymes causing debridement, hyperbaric oxygen therapy, cultured skin substitutes, and other wound therapies have been put forward. All of these therapies are associated with significant cost and are being used in some situations without sufficient evidence in favour of their efficacy.⁴

Phenytoin as a topical application is used in many studies on ulcers caused by diabetic, and it is seen to stimulate

the granulation tissue formation within 2-7 days. The antibacterial activity of phenytoin is against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella*, and *Pseudomonas*.⁵ Phenytoin results in proliferation of fibroblasts, collagen deposition, new blood vessel formation, promotes granulation tissues formation, reduces the collagenase action, and bacterial contamination.⁶ However, there are some contradictory reports on the use of phenytoin as topical agent.⁷

The present study was conducted to assess the effect of topical phenytoin used as dressing with comparison to conventional moist wound dressing in the healing of diabetic ulcers and to see that whether it is better in the management of diabetic ulcers.

METHODS

A randomised control, open label trial was conducted in which 70 patients with diabetic foot ulcers admitted in the Department of Surgery in Government Medical College Patiala, were enrolled in this study after obtaining written informed Consent and ethical approval from Institutional ethical committee. The inclusion and exclusion criteria are as follows:

Inclusion criteria

Patients with chronic ulcers with non-insulin dependent diabetes mellitus.

Exclusion criteria

- Chronic non-healing wounds caused by other ailments
- Diabetes mellitus with gangrenous changes
- Wounds with bone pathology
- Other co-morbid conditions like renal failure, other immunocompromised states and other factors, which adversely affect wound healing

A total of 70 patients with diabetic foot ulcers satisfying all the inclusion criteria mentioned above were included in the study. Data collected was entered in the Case Record Forms (CRF) after obtaining the written informed consent. The patients were divided randomly in study and the control group. The study group included the patients with wound care done with topical phenytoin therapy while control group patients were subjected to conventional wound care. After detailed clinical examination and relevant investigations, wounds were thoroughly debrided under anesthesia and the ulcer size as well as the surface area was assessed immediately after surgical debridement. Reassessment of the same was done after 10-14 days in both groups. Dressings were changed once daily in both groups. A 100 mg phenytoin sodium capsule was mixed in normal saline and applied locally and wound was covered with aseptic precautions. Conventional Dressing was done with 5% Betadine (Povidone-Iodine) solution. Daily monitoring of blood

sugar was done and accordingly appropriate treatments were provided. Statistical Analysis was done using Chi-Square test and p value was calculated.

RESULTS

Table 1: Gender wise distribution of the patients.

Treatment Group	Gender	No. of patients	Total
Group1 (Phenytoin) n=35	Male	22	35
	Female	13	
Group2 (Conventional) N=35	Male	18	35
	Female	17	

Table 1 shows the Gender wise distribution of the patients which were allocated the 2 groups that is group1 includes the patients who were treated with phenytoin topical preparation and includes 22 male and 13 female patients and Group2 includes the patients who were treated with the Conventional Dressings and includes 18 male and 17 female patients.

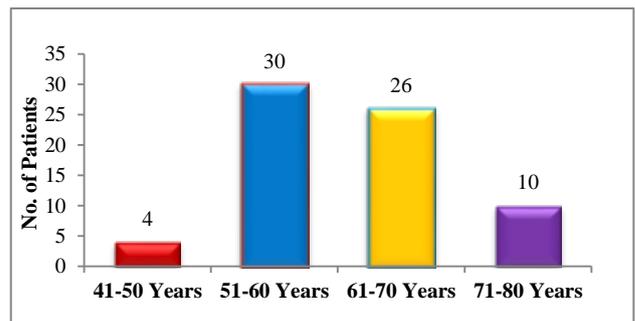


Figure 1: Age wise distribution of the patients.

Figure 1 shows the age wise distribution of the patients in this study. 30 patients were having foot complications of Diabetes in this study followed by the age group of 61-70 years having 26 patients, followed by the age group of 71-80 years age group having 10 patients and the least affected group with foot complications of diabetes mellitus was 41-50 years age group having 4 patients.

Table 2: Distribution of patients based on duration of hospital stay.

Treatment groups	Mean hospital stay (in Days)	Standard deviation	p value
Group 1 (Phenytoin) n=35	33.4	3.12	<0.05
Group 2 (Conventional) n= 35	39.7	4.39	<0.05

Table 2 shows the distribution of patients based on their Hospital stay and in Group1 patients who were treated with topical Phenytoin the Mean hospital stay in days was 33.4 with a standard deviation of 3.12 days.

Similarly in Group 2 patients who were treated with conventional method the mean hospital stay in days was 39.7 with a standard deviation of 4.39 days and the p value was <0.05 which was statistically significant.

Table 3: Distribution of patients based on the histopathological and clinical examination findings after 2 weeks of treatment.

Treatment groups	Histopathological and clinical findings of healthy granulation tissue in mean percentage	Standard deviation	p value
Group 1 (Phenytoin) n=35	89.2%	3.2	<0.05
Group 2 (Conventional) n= 35	73.9%	5.3	<0.05

Table 4: Comparison of various studies with this study.

Name of Study	Results/ Conclusion
Vardhan A et al	Phenytoin topical dressing decreases Hospital Stay and help in granulation tissue formation much earlier than conventional dressings and hence it is better than Conventional dressing with saline and Povidone – iodine.
Muthukumarswamy et al ⁵	Mean healing Time Better in phenytoin treated group than conventional methods.
Pendse et al ¹²	Phenytoin has significant antibacterial properties. 50% wounds treated with phenytoin had negative bacterial culture on 7th day of treatment, where as in the control group only 17% had negative culture.
Anstead et al ¹³	Phenytoin has promoted healing in a massively necrotized Grade IV decubitus ulcer not responding to any other therapy.
DaCosta et al ⁶	Phenytoin enhances the fibroblast infiltration with neovascularization and 2647 ignify cantly increases the tensile strength of healed wounds.
Pai et al ¹⁴	Good granulation tissue with topical phenytoin.
Tauro LF et al ¹⁵	Phenytoin aids in faster healing of diabetic wounds with better graft take up and decreased hospital stay.
Jayalal JA et al ¹⁶	Enhanced wound healing and sense of well-being in individuals with diabetic foot ulcer treated with topical application of phenytoin than the other classical wound dressing materials.

Table 3 shows the distribution of patients based on their histopathological and clinical examination after 2 weeks of treatment completion. In Group1 patients Healthy granulation tissue a seen in mean 89.2% patients with a standard deviation of 3.2 and in Group 2 patients healthy granulation tissue was seen in Mean 73.9% Patients with a standard deviation of 5.3 and both the groups had p value of <0.05 which is statistically significant.

DISCUSSION

Phenytoin is under investigation as a treatment for more than 100 diseases. Numerous allergy and proliferative, idiosyncratic cutaneous side effects have been reported with its use.⁸ A frequent observed and unwanted side effect of phenytoin, is gingival (Gum) hyperplasia, especially in children.⁹ Phenytoin promotes wound healing by following mechanisms: fibroblast proliferation, enhanced and rapid formation of granulation tissue, decreasing collagenase activity, glucocorticoid activity inhibiting, antibacterial activity by affecting inflammatory cells, neovascularisation and phenytoin increases gene expression of the platelet

derived growth factor β chain in macrophage and monocytes.^{10,11}



Figure 2: A case of diabetic foot ulcer at the time of admission in surgery ward of government medical college, Patiala.

In this study conducted in Government Medical College Patiala it was seen that mean hospital stay in days was less as compared to conventional treatment methods and

healthy granulation tissue after 2 weeks of treatment was seen in more patients treated with Phenytoin group as compared to conventional Dressing materials.

A case of diabetic foot ulcer

Figure 2 - 4 shows a 51 year old male patient admitted in Government medical college Patiala showing improvement after 2 weeks of treatment.



Figure 3: The same case after 2 weeks of topical phenytoin dressing showing improvement with decreased slough and healthy granulation tissue formation.

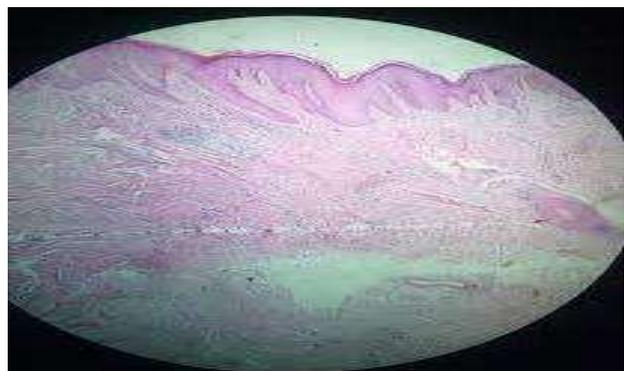


Figure 4: Histopathological examination of the skin sample after 2 weeks of treatment showing healthy granulation tissue formation.

CONCLUSION

This prospective randomized control study shows enhanced wound healing and sense of well-being in individuals with diabetic foot ulcer treated with topical application of phenytoin than the conventional agents like use of normal saline and povidone-iodine in the wound dressings.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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