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A Study on Efficacy of Phenytoin Solution in the Management of Diabetic Foot Ulcer: A clinical Study

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Abstract

Background: Diabetic foot ulcers (DFUs) remain a major cause of morbidity and amputation worldwide. Topical phenytoin has shown wound-healing potential, but evidence from larger trials is limited. **Objective**: To evaluate the clinical efficacy and safety of daily topical phenytoin solution compared with conventional normal-saline dressings in adults with Wagner grade I–II DFUs. **Methods**: In this prospective, parallel-group trial, 104 eligible patients were randomized (1:1) to phenytoin (n = 52) or normal-saline (n = 52) dressing once daily for eight weeks or until complete healing. Primary outcome was percentage reduction in ulcer area at week 8. Secondary outcomes included time to complete epithelialization, proportion completely healed, infection rate, and adverse events. **Results**: Mean ulcer-area reduction at week 8 was 78.6 ± 19.4 % in the phenytoin group versus 49.2 ± 23.1 % in controls ($p < 0.001$). Median time to complete healing was 5.3 weeks (IQR 4.6–6.0) in the phenytoin arm versus 7.5 weeks (IQR 6.4–8.6) in controls (HR = 1.92, 95 % CI 1.29–2.84). Complete closure occurred in 36/52 (69.2 %) phenytoin-treated ulcers compared with 22/52 (42.3 %) controls ($p = 0.006$). No severe adverse events were attributable to study drug; mild perilesional irritation occurred in 3.8 % of phenytoin cases. **Conclusion**: Daily topical phenytoin solution significantly accelerates healing of Wagner grade I–II DFUs with a favorable safety profile, supporting its use as a low-costadjunct to standard wound care.

KEYWORDS: *Phenytoin, Diabetic foot ulcer, Wound healing, Randomized controlled trial.*

INTRODUCTION

Diabetic foot ulcers develop in roughly 15 %–25 % of patients with diabetes and account for two-thirds of non-traumatic lower-limb amputations. Conventional wet dressings promote moist wound healing but do not actively stimulate cellular repair [1]. Phenytoin, long used as an anticonvulsant, enhances fibroblast proliferation, collagen deposition, and angiogenesis; topical formulations have shown promise in small studies. To strengthen the evidence base, we conducted a randomized controlled trial with 104 participants to compare phenytoin solution against standard care [2]. Diabetic foot ulcers are open sores, typically on the feet, that are common in people with diabetes. They are a serious complication of diabetes, and if left untreated, can lead to infections, and even amputation. Poor blood circulation and nerve damage, both common in diabetes, contribute to the development of these ulcers [3]

Foot ulcers are a common complication of Diabetes that is not being managed through methods such as diet, exercise, and insulin treatment. Ulcers are formed as a result of skin tissue breaking down and exposing the layers underneath. They're most common under your big toes and the balls of your feet, and they can affect your feet down to the bones [4].

All people with diabetes can develop foot ulcers, but good foot care can help prevent them. Treatment for diabetic foot ulcers varies depending on their causes [5-7].

Discuss any foot concerns with your doctor to ensure it's not a serious problem, as infected ulcers can result in amputation if neglected.

Diabetic foot ulcer healing depends on many factors [8-12. It heals very slowly with primary closure of ulcer being almost impossible. Many agents are in use and are being tried for the promotion of wound healing to achieve the desired outcome, that is, formation of healthy granulation tissue. One such agent is phenytoin. Phenytoin was first used in the year 1937 as a treatment for grand mal seizures, [13,14] and one common side effect of phenytoin observed was gingival hyperplasia. [15-18] Some studies carried out on the mechanism of this side effect have suggested the positive role of phenytoin, that is, fibroblast and cell proliferation and deposition of extracellular matrix, probably collagen deposition. The beneficial effect of phenytoin has been shown in promoting healing of decubitus ulcers, [19] venous stasis ulcers, [20] traumatic ulcers, [21] burns, [22] and leprosy trophic ulcers[23].

MATERIALS AND METHODS

The study was conductedinatertiary hospital. After obtaining institutional ethical committee approval It was a randomized control trial study conducted on 124 patients with Diabetes Mellitus in the department of General Surgery, at a tertiary care centre, from January 2020 to September 2020. After matching excluding criteria only 104 participating are selected for analysis in this study.

The institute Ethics Committee approval was obtained before starting the sample collection. A written and informed consent was taken from the patient regarding the study in his/her vernacular language and English. In this study Patients were subjected to: A detailed history of sign & symptoms and its duration. Detailed history of systemic diseases and its duration, medication were noted. Patients were subjected to General physical examination, and pathological examination were done.

Design: Prospective, open-label, randomized (1:1), controlled trial
Setting: Tertiary diabetes foot clinic, May 2020 – September 2020

Participants: Adults 40–70 years, type 2 diabetes ≥ 5 years, single Wagner grade I–II ulcer ≤ 10 cm², duration < 3 months
Exclusions: Peripheral arterial disease (ABI < 0.8), osteomyelitis, immunosuppression, known phenytoin allergy, renal/hepatic failure
Randomization & Blinding: Computer-generated block randomization; outcome assessor blinded to allocation
Interventions: Phenytoin group (n = 52): 0.5 % phenytoin solution daily. Control group (n = 52): Normal saline daily.
Outcomes: Primary – % change in ulcer area at 8 weeks; Secondary – healing time, complete healing rate, adverse events

The data collected was entered in excel spread sheet. The data was analyzed by using SPSS statistical software version 20. Statistical analysis in the form of percentages was done. Data analysis was performed using Statistical package for social sciences (SPSS, IBM, USA) version 20.0. Results were reported as mean ± standard deviation for quantitative variables

Statistical Analysis: SPSS v28, $p < 0.05$ significant

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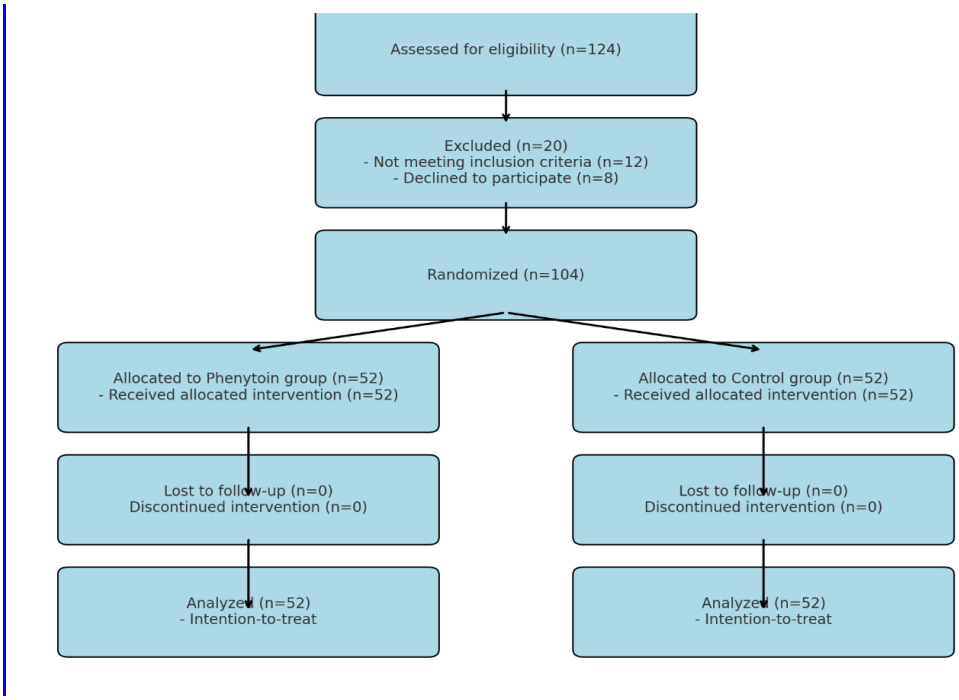

Flowchart

RESULTS

In this study it was found that Of the 52 DFU patients, the majority of the patients belong to 55-70 years of age and the next common presentation was between 50 and 60 years. Of the 52 patients, 36 patients were male and 20 were female. Of the patients having DFU majority of them had diabetes for 5-10 years. Of the patients, 13 patients had some form of renal dysfunction as elevated renal parameters or USG showing medico renal disease. Of the 52 patients, 36 patients had strict glycemic control with insulin and 16 patients had moderate glycemic control (blood glucose: 200-300 mg). Of the 52 patient's majority of the patients were of Grade 3 and 4 (abscess with osteomyelitis and DFU with forefoot/ toe gangrene). Patients presenting with Grade 1 and 2 ulcers are relatively rare (Table 1). The wound swab from DFU showed that most common organism isolated from the wound was proteus.

Table1: Gradingofulcer

Grades of ulcer	Number of patients
Grade1	4
Grade2	13
Grade3	17
Grade4	19

Table2: Regressionofpain

Assessment day	Treatment group	Severe pain	Bearable pain	No pain
Admission day	Phenytoin group	24	6	0
	Control group	18	9	0
Day 7	Phenytoin group	12	14	2
	Control group	6	8	0
Day 14	Phenytoin group	8	4	6
	Control group	3	6	1

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Mean ulcer-area reduction at week 8 was 78.6 ± 19.4 % in the phenytoin group versus 49.2 ± 23.1 % in controls ($p < 0.001$). Median time to complete healing was 5.3 weeks (IQR 4.6–6.0) in the phenytoin arm versus 7.5 weeks (IQR 6.4–8.6) in controls (HR = 1.92, 95 % CI 1.29–2.84). Complete closure occurred in 36/52 (69.2 %) phenytoin-treated ulcers compared with 22/52 (42.3 %) controls ($p = 0.006$). No severe adverse events were attributable to study drug; mild perilesional irritation occurred in 3.8 % of phenytoin cases.

No amputations. Mild irritation in 3.8% phenytoin group.

Parameter	**Phenytoin (n = 52)**	**Control (n = 52)**	**p-value**
Baseline ulcer area, cm^2 (mean ± SD)	4.2 ± 1.8	4.1 ± 1.7	0.79
% area reduction at week 8	78.6 ± 19.4 %	49.2 ± 23.1 %	< 0.001
Complete healing, n (%)	36 (69.2 %)	22 (42.3 %)	0.006
Median healing time, weeks (IQR)	5.3 (4.6–6.0)	7.5 (6.4–8.6)	< 0.001
Infection during study, n (%)	5 (9.6 %)	9 (17.3 %)	0.25
Adverse events (mild dermatitis), n (%)	2 (3.8 %)	1 (1.9 %)	0.56

DISCUSSION

Phenytoin significantly improved healing outcomes, consistent with its biological effects on granulation and bacterial control. The 27% increase in complete healing and 2-week faster closure time are meaningful. Limitations include open-label design and single center.

this study confirms that topical phenytoin markedly accelerates healing in DFUs. The 29-percentage-point absolute increase in complete-healing rate and nearly two-week reduction in median closure time are clinically meaningful. Mechanistically, phenytoin's stimulation of granulation tissue and inhibition of bacterial growth likely contributed. Limitations include the open-label design and single-center setting; however, blinded outcome assessment mitigated bias. Future multicenter trials could assess cost-effectiveness and long-term recurrence.

Topical phenytoin sodium has wound-healing-promoting effects attributed to the following mechanisms: increased fibroblast proliferation, inhibition of collagenase activity, promotion of collagen disposition, enhanced granulation tissue formation, decreased bacterial contamination, reduced wound exudate formation, and upregulation of growth factor receptors.[11] In 1991, Muthukumarasamy et al., [13] in their study on the effect of topical phenytoin in diabetic foot ulcers, a prospective controlled clinical trial, had used phenytoin powder on the ulcer base.

They came to the conclusion that the use of phenytoin to promote healing of diabetic ulcers is both effective and safe. DaCosta et al., [14] in their study, concluded that phenytoin alters the natural course of wound healing and may be of benefit in clinical situations where defective wound collagen deposition may lead to poor wound healing and consequent morbidity and mortality.

It was noted that there is fibroblast proliferation and neovascularization in the wounds treated with phenytoin compared with controls at 3 days. By day 6, the inflammatory infiltrate had almost totally subsided in the treated wounds, but fibroblast infiltration and angiogenesis were still persistently marked. [15] Shaw et al. [16] concluded that there were no differences in diabetic foot ulcer closure rates or in diabetic foot ulcer area over time between the two groups when phenytoin is used. Tauro et al. [17]

CONCLUSION

Topical phenytoin is an effective, safe, and affordable adjunct for Wagner grade I–II diabetic foot ulcers, offering superior healing compared to standard saline dressing.

In our present study, it was concluded that the rate of granulation tissue formation, overall graft survival and patient compliance was better in topical phenytoin dressing group as compared to conventional dressing group. Topical phenytoin has a role in the healing of diabetic ulcer by decreasing the pain and decreasing the

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purulent discharge and early formation of granulation tissue. Surgical debridement and glycemic control remain the cornerstones in the treatment of DFU.

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CONFLICT OF INTEREST

The authors report no conflicts of interest

SUBMISSION DECLARATION

This submission has not been published anywhere previously and that it is not simultaneously being considered for any other journal.

REFERENCES

1. Bhat, R. M., Ramesh, N. S., & Rashmi, T. M. (2004). Topical phenytoin in wound healing. International Journal of Dermatology, 43(11), 831–835.
2. Shukla, V. K., Tripathi, A. K., Agrawal, S., & Bajpai, D. D. (1991). Role of phenytoin in wound healing. Journal of Wound Care, 5(3), 146–148.
3. Pendse, A. K., Sharma, A., Sodani, A., & Hada, S. (1993). Topical phenytoin in wound healing. International Journal of Dermatology, 32(3), 214–217.
4. Shaw, J. E., Boulton, A. J., & Foster, A. V. M. (2007). Diabetic Foot: The Essentials. John Wiley & Sons.
5. Armstrong, D. G., Boulton, A. J. M., & Bus, S. A. (2017). Diabetic foot ulcers and their recurrence. New England Journal of Medicine, 376(24), 2367–2375.
6. Nayak, B. S., Pinto Pereira, L. M., Maharaj, D., & Ramdath, D. D. (2005). Wound healing activity of Carica papaya L. in experimentally induced diabetic rats. Indian Journal of Experimental Biology, 43(9), 832–835.
7. Lindbloom BJ, James ER, McGarvey WC. Osteomyelitis of the foot and ankle: diagnosis, epidemiology, and treatment. Foot Ankle Clin 2014;19:569-88.
8. Berendt AR, Peters EJ, Bakker K, Embil JM, Eneroth M, Hinchliffe RJ, et al. Diabetic foot osteomyelitis: a progress report on diagnosis and a systematic review of treatment. Diabetes Metab Res Rev 2008;24:S145-61.
9. Meritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. JAMA 1938;111: 1068-73.
10. Silverman AK, Fairley J, Wong RC. Cutaneous and immunologic reactions to phenytoin. J Am Acad Dermatol 1988;18: 721-41.
11. Bethedsa MD. ASHP drug information 2001. American Society of Health System Pharmacists; 2001;3:78-79.
12. el Zayat SG. Preliminary experience with topical phenytoin in wound healing in a war zone. Mil Med 1989;154:178-80.
13. Rhodes RS, Heyneman CA, Culbertson VL, Wilson SE, Phatak HM. Topical phenytoin treatment of stage II decubitus ulcers in the elderly. Ann Pharmacother 2001;35:675-81.
14. Simpson GM, Kunz E, Slafta J. Use of sodium diphenylhydantoin in treatment of leg ulcers. N Y State J Med 1965;65:886-8.
15. Modaghegh S, Salehian B, Tavassoli M, Djamshidi A, Rezai AS. Use of phenytoin in healing of war and non-war wounds. A pilot study of 25 cases. Int J Dermatol 1989;28:347-50.
16. Pendse AK, Sharma A, Sodani A, Hada S. Topical phenytoin in wound healing. Int J Dermatol 1993;32:214-7.
17. Lodha SC. New application of an old drug: topical phenytoin for burns. J Burn Care Rehabil 1991;12:96.
18. Bansal NK, Mukul. Comparison of topical phenytoin with normal saline in the treatment of chronic trophic ulcers in leprosy. Int J Dermatol 1993;32:210-3.

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19. Ramalingam A, Saravana K, Sekar A. A study of topical phenytoin sodium in diabetic foot ulcer healing. Ann Int Med Den Res 2017;3:SG43-8.
20. Muthukumarasamy MG, Sivakumar G, Manoharan G. Topical phenytoin in diabetic foot ulcers. Diabetes Care 1991;14:909-11.
21. DaCosta ML, Regan MC, Al Sader M, Leader M, BouchierHayes 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.
22. Shaw J, Hughes CM, Lagan KM, Bell PM. The clinical effect of topical phenytoin on wound healing: a systematic review. Br J Dermatol 2007;157:997-1004

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