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Topical Phenytoin versus Normal Saline Dressing for Diabetic Foot Ulcer Healing: A Randomized Prospective Comparative Study from a Tertiary Care Centre in Western India

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Abstract

Background: Diabetic foot ulcers (DFUs) remain a leading cause of hospitalization and lower-limb amputation worldwide, and conventional dressings such as normal saline offer limited acceleration of healing. Topical phenytoin has been proposed as a low-cost adjunct that promotes fibroblast proliferation, collagen deposition, and angiogenesis, but evidence for its efficacy in DFUs remains inconsistent.

Objective: To compare the efficacy of topical phenytoin dressing with conventional normal saline dressing in promoting wound healing and granulation tissue formation in patients with DFUs at a tertiary care centre.

Methods: In this prospective, randomized, open-label comparative study, 66 patients with DFUs presenting to the Department of General Surgery between June 2024 and December 2025 were randomized by lottery method (1:1) into two groups of 33 each: Group A received

phenytoin-soaked gauze dressing (dose titrated to ulcer size) and Group B received conventional normal saline dressing, both changed daily. Ulcer surface area, granulation tissue quality, and healing rate were assessed on days 1, 7, 14, and 21. Categorical variables were compared using the chi-square test and continuous variables using an independent-samples t-test; $p<0.05$ was considered significant.

Results: Baseline age, sex, glycated hemoglobin, and ulcer area were comparable between groups ($p>0.05$). By day 21, healthy granulation tissue was present in 78.8% of the phenytoin group versus 12.1% of the saline group ($p<0.001$). Mean percentage ulcer area reduction was 71.45% with phenytoin versus 32.09% with saline, and mean healing rate was 378.2 mm^2/day versus 163.4 mm^2/day, respectively ($p<0.001$ and $p=0.001$). All phenytoin-treated patients achieved >50% area reduction versus none in the saline group. Adverse effects were limited to transient application-site discomfort, which resolved with dilution of the preparation.

Conclusion: Topical phenytoin dressing significantly accelerated granulation tissue formation and wound contraction compared with normal saline in DFUs, with a favourable safety profile. It represents an inexpensive, accessible adjunct for DFU management, particularly in resource-limited settings, although larger, blinded, multicentre trials are needed to confirm these findings.

Keywords: Diabetic Foot; Phenytoin, Wound Healing, Bandages, Granulation Tissue, Randomized Controlled Trial.

Introduction

Diabetic foot ulcers (DFUs) are among the most disabling and costly complications of diabetes mellitus. An estimated 19% to 34% of people with diabetes will develop a foot ulcer in their lifetime, and roughly one in five of these ulcers culminates in lower-extremity amputation.1 In India, home to one of the largest populations of people with diabetes globally, foot ulceration is disproportionately severe: DFUs are reported to account for a large majority of non-traumatic lower-limb amputations, and the economic burden per episode of care is substantial for a health system in which out-of-pocket expenditure predominates.2 Beyond the risk of amputation, DFUs are associated with recurrent hospitalization, impaired quality of life, and excess long-term mortality, underscoring the urgency of identifying wound-care strategies that are both clinically effective and affordable in resource-constrained settings.

The pathophysiology of DFU formation is multifactorial, arising from the convergence of peripheral sensorimotor and autonomic neuropathy, macro- and microvascular insufficiency, and impaired immune surveillance, which together predispose the foot to unrecognized trauma, poor perfusion, and delayed, dysregulated healing.3 Once ulceration occurs, chronic wounds frequently become arrested in a prolonged inflammatory phase, characterized by persistently elevated proteases, senescent fibroblasts, and deficient angiogenesis, all of which impede the transition to productive granulation tissue formation.

Contemporary management of DFUs rests on established principles of glycemic optimization, infection control, surgical debridement, and offloading, supplemented by a wide array of adjunctive wound-bed preparation techniques and dressings. However, the 2023 update to the International Working Group on the Diabetic Foot (IWGDF) guideline on wound healing interventions concluded that, for most adjunctive topical and biological therapies, the certainty of evidence remains low, reflecting small trial sizes, heterogeneous outcome definitions, and inconsistent risk-of-bias reporting across

the field.4 This evidentiary gap is particularly notable for topical phenytoin, an anticonvulsant repurposed for wound care on the basis of incidental observations of gingival and dermal fibrous overgrowth in patients on long-term therapy.

Mechanistically, phenytoin is thought to accelerate wound healing through several complementary pathways: stimulation of fibroblast proliferation and collagen synthesis, promotion of early and marked angiogenesis, reduction of collagenase activity, and an antibacterial effect against common wound pathogens.5,6 These properties have been explored across a range of chronic wound types, beginning with Muthukumarasamy and colleagues' controlled inpatient study of topical phenytoin in DFUs, which reported accelerated healing relative to conventional dressing.7 Subsequent double-blind work by Pai and colleagues corroborated this benefit in a controlled Indian cohort.8

Nonetheless, the evidence base has remained contested. A rigorously conducted double-blind randomized controlled trial by Shaw and colleagues found only a modest, non-significant advantage for topical phenytoin over placebo gel in DFU healing, raising the possibility that earlier open-label results overstated the treatment effect.9 A meta-analysis pooling thirteen studies and 980 patients with ulcers of varied etiology reported a significant benefit of phenytoin for complete wound healing (odds ratio 3.03, 95% CI 2.23–4.10), yet heterogeneity in study quality limited confidence in this pooled estimate.10 Most recently, a 2025 systematic review identified 23 studies of phenytoin in DFUs, of which 20 reported a favourable effect; however, the majority were unblinded, lacked a priori sample-size calculation, or did not adequately describe randomization, precluding formal meta-analysis and explaining the IWGDF's continued reluctance to endorse phenytoin as standard care.11 Against this backdrop of methodologically variable but directionally consistent evidence, well-designed randomized studies from diverse settings remain valuable in clarifying whether topical phenytoin offers a genuine, reproducible clinical benefit.

Given the high burden of DFUs in India, the low cost and wide availability of phenytoin, and the persisting uncertainty in the literature, we conducted a prospective randomized comparative study to evaluate the efficacy of topical phenytoin dressing against conventional normal saline dressing in patients with DFUs at a tertiary care centre in Rajasthan, India. Our primary objective was to compare the rate of wound healing between the two dressing modalities, and our secondary objective was to compare granulation tissue formation, with the intention of generating pragmatic, real-world evidence relevant to resource-limited surgical practice.

Materials and Methods

Study design, setting, and duration

This was a prospective, randomized, open-label, comparative study conducted in the Department of General Surgery, J.L.N. Medical College and Associated Group of Hospitals, Ajmer, Rajasthan, India. Patients were recruited from the Surgery Outpatient Department and Emergency Department between 1 June 2024 and 31 December 2025. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants after the study protocol was explained in their preferred language.

Participants

Adults presenting with a diabetic foot ulcer were eligible for inclusion. Patients older than 70 years, those with uncontrolled bleeding disorders, and those who were immunocompromised (on immunosuppressive therapy,

HIV-positive, or with active malignancy) were excluded. Baseline assessment included a detailed history and clinical examination, glycated hemoglobin (HbA1c), routine hematological and biochemical investigations, and wound culture and sensitivity testing.

Sample size and randomization

The sample size was calculated using the standard formula for comparison of proportions ($n = Z^2pq/d^2$), assuming an estimated DFU prevalence of 10% in the Indian population, a 95% confidence level (Z = 1.96), and a permissible error of 5%, yielding a required sample of 66 patients. Participants were allocated in a 1:1 ratio to Group A (phenytoin dressing, n = 33) or Group B (normal saline dressing, n = 33) using simple randomization by the lottery method.

Intervention

In Group A, a phenytoin suspension was freshly prepared from crushed phenytoin tablets, with the dose titrated to ulcer surface area: 100 mg for ulcers of 0–5 cm^2, 150 mg for 5.1–9 cm^2, 200 mg for 9.1–15 cm^2, and 300 mg for ulcers exceeding 15 cm^2. Sterile gauze soaked in this suspension was applied directly to the debrided ulcer bed and changed daily. In Group B, the ulcer was dressed daily with sterile gauze soaked in normal saline. In both groups, systemic antibiotics were prescribed according to culture and sensitivity results when clinically indicated, and blood glucose was monitored and optimized throughout the treatment period to avoid confounding of the healing response by glycemic control.

Outcome measures

The primary outcome was the rate of ulcer healing, quantified as ulcer surface area reduction (in mm^2 per day) between day 1 and day 21. Secondary outcomes were the proportion of patients developing healthy granulation tissue and the percentage reduction in ulcer surface area at day 21. Ulcer dimensions and granulation tissue characteristics (absent, pale, or healthy/good) were recorded on days 1, 7, 14, and 21 by clinicians blinded to group allocation status at the time of measurement wherever feasible.

Statistical analysis

Continuous variables (age, HbA1c, ulcer area, healing rate) were summarized as means and compared between groups using the independent-samples t-test. Categorical variables (sex distribution, granulation tissue grade, banded ulcer-area categories) were compared using the chi-square test. A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using standard statistical software.

Results

Sixty-six patients with DFUs were enrolled and randomized equally into the phenytoin (n=33) and normal saline (n=33) groups. Baseline demographic and clinical characteristics were comparable between the two groups (Tables 1–3). The cohort had a male predominance (65.2% overall), consistent with previously reported sex distributions in Indian DFU populations, and age ranged from 30 to 79 years with no significant between-group difference (p=0.127). Baseline glycemic control, stratified by HbA1c band, was also statistically comparable between groups (p=0.698), reducing the likelihood that differential glycemic control confounded the healing outcomes observed.

At baseline (day 1), granulation tissue was absent in all 66 patients in both groups, confirming equivalent starting wound conditions (Table 4). Mean initial ulcer surface area was likewise comparable between the phenytoin group (118.1 cm^2) and the saline group (109.4 cm^2) (Table 6).

By day 21, a marked divergence in healing trajectory was evident between groups. Healthy granulation tissue had developed in 26 of 33 patients (78.8%) receiving phenytoin dressing, compared with only 4 of 33 patients (12.1%) receiving saline dressing ($p<0.001$; Table 5). The mean final ulcer area was significantly smaller in the phenytoin group (38.7 cm^2) than in the saline group (75.1 cm^2) ($p<0.001$; Table 7), corresponding to a mean percentage area reduction of 71.45% with phenytoin versus 32.09% with saline (Table 10).

The mean healing rate was 378.2 mm^2/day in the phenytoin group compared with 163.4 mm^2/day in the saline group ($p=0.001$; Table 8); higher-velocity healing bands (≥300 mm^2/day) were occupied almost exclusively by phenytoin-treated patients. Consistently, all 33 patients (100%) in the phenytoin group achieved more than 50% reduction in ulcer area by day 21, compared with none of the 33 patients in the saline group, of whom 32 (97%) remained within the 26–50% reduction band ($p<0.001$; Table 9).

Apart from transient discomfort during dressing application in a subset of patients in the early phase of the study — which resolved after appropriate dilution of the phenytoin preparation — no significant local or systemic adverse effects attributable to phenytoin dressing were observed.

Editorial note: The original thesis dataset labels Table 1 with a total of N=40 and subgroup headers of n=20, while the tabulated row values (8+8+9+8=33 and 5+13+6+5+4=33) and every subsequent table consistently use n=33 per group (N=66). This manuscript has standardized all group sizes to n=33 (N=66) throughout; the authors should verify the original source data to confirm this correction before submission.

Table 1. Distribution of patients by age group

Age range (years)	Phenytoin (n=33)	Normal saline (n=33)	p value
30–39	8	5	
40–49	8	13	
50–59	9	6	
60–69	8	5	
70–79	0	4	0.127

Table 2. Distribution of patients by sex

Sex	Phenytoin (n=33)	Normal saline (n=33)	p value
Male	22	21	
Female	11	12	0.793

Table 3. Distribution of patients by HbA1c level

HbA1c range (%)	Phenytoin (n=33)	Normal saline (n=33)	p value
5.5–6.7	15	13	

HbA1c range (%)	Phenytoin (n=33)	Normal saline (n=33)	p value
6.8–6.9	11	10	
7.0–7.5	7	10	0.698

Table 4. Granulation tissue status at day 1 (baseline)

Granulation tissue	Phenytoin (n=33)	Normal saline (n=33)	p value
Absent	33	33	
Present (pale/healthy)	0	0	1.000

Table 5. Granulation tissue status at day 21

Granulation tissue	Phenytoin (n=33)	Normal saline (n=33)	p value
Healthy (good)	26 (78.8%)	4 (12.1%)	
Pale	7 (21.2%)	29 (87.9%)	<0.001

Table 6. Initial ulcer surface area before treatment

Surface area (cm²)	Phenytoin (n=33)	Normal saline (n=33)	p value
0–49	15	0	
50–99	7	15	
100–149	3	13	
>150	8	5	
Mean (cm²)	118.1	109.4	0.681

Table 7. Final ulcer surface area after treatment (day 21)

Surface area (cm²)	Phenytoin (n=33)	Normal saline (n=33)	p value
0–49	25	4	
50–99	4	22	
100–149	3	6	
>150	1	1	
Mean (cm²)	38.7	75.1	<0.001

Table 8. Distribution of patients by healing rate

Healing rate (mm²/day)	Phenytoin (n=33)	Normal saline (n=33)	p value
<150	4	16	
150–299	16	17	
300–499	6	0	
≥500	7	0	
Mean (mm²/day)	378.2	163.4	0.001

Table 9. Distribution of patients by percentage area reduction at day 21

Area reduction (%)	Phenytoin (n=33)	Normal saline (n=33)	p value
0–25	0	1	
26–50	0	32	
>50	33	0	<0.001

Table 10. Mean reduction in ulcer area at day 21

Parameter	Phenytoin (n=33)	Normal saline (n=33)
Mean % area reduction	71.45%	32.09%
Mean final ulcer area (cm²)	38.72	75.11

Discussion

In this randomized prospective comparative study of 66 patients with DFUs, topical phenytoin dressing produced substantially greater wound contraction, faster healing rates, and superior granulation tissue formation than conventional normal saline dressing. These findings, obtained under baseline demographic and glycemic conditions that were statistically comparable between arms, support the hypothesis that the observed benefit is attributable to the local pharmacological action of phenytoin rather than to confounding differences in age, sex, or diabetic control.

The magnitude of benefit we observed — a mean area reduction of 71.45% versus 32.09%, and a nearly six-fold higher proportion of patients achieving healthy granulation tissue by day 21 — is biologically plausible given phenytoin's established actions on wound biology. Experimental work by DaCosta and colleagues demonstrated that diphenylhydantoin sodium promotes early, marked angiogenesis and increases collagen deposition and tensile strength in healing wounds, while Moy and colleagues showed that phenytoin modulates fibroblast proliferation and connective tissue metabolism in human skin cultures.5,6 These mechanisms plausibly

underlie the accelerated transition from an inflammatory to a proliferative wound phase that we observed clinically. Our results are consistent with the earliest controlled evaluations of topical phenytoin in DFUs. Muthukumarasamy and colleagues first reported accelerated healing with phenytoin dressing in an inpatient cohort, and Pai and colleagues subsequently confirmed a significant benefit in a double-blind controlled trial.7,8 More recent Indian studies mirror our findings closely: Patil and colleagues, in a randomized trial of 100 patients with Grade I/II DFUs, reported significantly reduced wound discharge and slough with phenytoin dressing and a shorter mean hospital stay (20 versus 26 days) compared with saline dressing.12 Babu and colleagues, in a longitudinal comparative study of 100 patients with chronic DFUs, likewise demonstrated superior granulation tissue formation and faster surface-area reduction with phenytoin dressing relative to saline.13 A 2024 comparative study by Tabana and colleagues similarly reported improved healing outcomes with topical phenytoin in neuropathic DFUs with mild infection.14 The consistency of these effect directions across studies conducted a decade or more apart, and across differing patient populations, strengthens the plausibility of a genuine treatment effect.

At the same time, our findings must be interpreted against a more heterogeneous evidence landscape. Shaw and colleagues' double-blind, placebo-controlled randomized trial — among the most methodologically rigorous studies in this field — found only a modest and statistically non-significant advantage for phenytoin over control gel in DFU healing.9 This discrepancy with the largely positive open-label literature, including our own findings, may partly reflect differences in blinding: open-label assessment of granulation tissue quality and wound photographs is susceptible to observer bias, a limitation our study shares with the majority of Indian trials in this area. A pooled meta-analysis of thirteen studies (980 patients with ulcers of varied etiology) found phenytoin significantly increased complete wound healing (odds ratio 3.03, 95% CI 2.23–4.10), yet a subsequent 2025 systematic review restricted to DFUs found that, of 23 eligible studies, 17 lacked blinding, 10 did not adequately describe randomization, and only one performed an a priori sample-size calculation — precluding meta-analysis and underlying the IWGDF's continued position that current evidence does not support routine use of phenytoin in DFU care.10,11,4 Our study addresses some, but not all, of these methodological gaps: randomization was performed prospectively with a pre-specified, formula-based sample size, and outcomes were assessed at standardized intervals, but the open-label design and single-centre setting remain important limitations shared with most of the existing literature.

From a clinical and health-systems perspective, the accelerated healing observed with phenytoin has practical implications beyond wound size alone. Faster granulation tissue formation shortens the interval to secondary closure or skin grafting and may reduce the duration of hospital-based wound care, an outcome corroborated by shorter reported hospital stays in comparable Indian cohorts.12,13 Given that phenytoin tablets are inexpensive, widely available even in peripheral health facilities, and require no specialized storage or application equipment, topical phenytoin dressing may be particularly well suited to resource-limited settings where access to advanced wound-care technologies such as negative-pressure therapy or bioengineered skin substitutes is constrained.

This study has several limitations that temper the strength of these conclusions. First, it was conducted at a single tertiary centre with a modest sample size and a relatively short 21-day follow-up window, limiting generalizability and precluding assessment of complete wound closure, recurrence, or long-term amputation-free survival. Second, the open-label design introduces potential observer bias in granulation tissue grading, despite efforts to standardize assessment. Third, several patients experienced application-site discomfort in the early phase of the study, which was managed by diluting the phenytoin preparation but may indicate a need for formal dose-tolerability optimization in future protocols. Finally, the healing-rate metric (mm^2/day) is sensitive to baseline ulcer size, and although mean baseline areas were statistically comparable between groups, larger studies with area-adjusted or time-to-healing analyses would provide more robust effect estimates.

Future research should prioritize adequately powered, multicentre, blinded randomized trials with standardized phenytoin formulations and dosing, extended follow-up to assess durable wound closure and recurrence, and structured cost-effectiveness analysis, in order to resolve the tension between the encouraging clinical trial literature and the more cautious position taken by international guideline bodies.

Conclusion

In this randomized prospective comparative study, topical phenytoin dressing was associated with significantly greater granulation tissue formation, wound contraction, and healing rate than conventional normal saline dressing in patients with diabetic foot ulcers, with a favourable and manageable safety profile. These findings support topical phenytoin as a low-cost, accessible adjunct for DFU wound care, particularly in resource-limited settings, while underscoring the need for larger, blinded, multicentre trials to establish its role in evidence-based guideline recommendations.

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