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COMPARATIVE STUDY OF THE EFFICACY OF TOPICAL INSULIN VERSUS TOPICAL PHENYTOIN IN THE HEALING OF CHRONIC DIABETIC FOOT ULCERS

General Surgery

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ABSTRACT

A prospective comparative study of 80 patients with Wagner Grade I and II diabetic foot ulcers comparing topical insulin and topical phenytoin dressings. Topical insulin demonstrated superior wound healing with greater percentage reduction in ulcer area compared with topical phenytoin. **Objectives:** To compare the efficacy of topical insulin versus topical phenytoin application in the healing of chronic diabetic ulcers, primarily in terms of rate of wound healing. **Methods:** This longitudinal comparative study was conducted in the Department of General Surgery at Sri Siddhartha Medical College and Hospital, Tumkur, over a 24-month period. Eighty patients with diabetes mellitus having Wagner grade I and II ulcers were included and divided into two groups of 40 each. Group A received topical insulin dressings, while Group B received topical phenytoin dressings. Both groups received standard wound care including glycemic control, debridement, off-loading, and infection control. Wound size was measured at baseline and weekly for four weeks. The primary outcome variable was ulcer healing rate, assessed by reduction in wound area. **Results:** The findings demonstrated a clinically meaningful superiority of topical insulin, with a higher mean percentage reduction in ulcer size (41.98%) compared to topical phenytoin (31.99%), and a significant intergroup difference ($p < 0.001$). **Conclusion:** Topical insulin is more effective than topical phenytoin in enhancing the healing of chronic diabetic ulcers.

KEYWORDS

Diabetic Foot Ulcer, Topical Insulin, Topical Phenytoin, Wound Healing

INTRODUCTION

Diabetes mellitus (DM) is a major global health burden, with impact on morbidity, mortality, and healthcare resources. The global prevalence of diabetes is projected to rise markedly in the coming decades, particularly in developing countries, so increasing the population at risk of diabetic complications [1]. One of the most troublesome, costly complications is development of chronic lower-limb ulcers particularly foot ulcers which are prone to delayed healing, infection, and amputation [2]. The lifetime risk of a person with diabetes developing a foot ulcer is around 19 % to 34 % [3]. Around 85 % of lower-extremity amputations in diabetic persons are preceded by a foot ulcer [4]. In the Indian context, it is estimated that some 40,000 legs are amputated annually, of which about three-quarters are neuropathic with secondary infection [5].

Chronic diabetic ulcers (CDUs) are wounds that fail to proceed through the normal physiologic phases of wound healing in a timely and orderly fashion. The standard phases of wound healing include hemostasis, inflammation, proliferation (granulation tissue formation, angiogenesis, epithelialization), and remodeling [6]. In diabetes, multiple derangements impair these processes: neuropathy reduces protective sensation and leads to repetitive trauma, peripheral arterial disease reduces perfusion, hyperglycemia and advanced glycation end-products impair cellular function, and microvascular dysfunction compromises nutrient and oxygen delivery [7]-[8]. At the cellular level, diabetic wounds have impaired macrophage and neutrophil function, decreased growth factor expression (e.g., VEGF, IGF1), reduced fibroblast and keratinocyte migration and proliferation, deficient angiogenesis, and reduced collagen deposition [9]-[10]. These factors delay wound closure, increase risk of infection, and ultimately heighten the likelihood of lower-extremity amputation.

In addition to clinical morbidity, diabetic foot ulcers pose a substantial economic burden. Conventional management involves repeated debridement, off-loading, infection control, advanced dressings, and even hospitalization or surgery [11]. Given the protracted healing times, high recurrence rates, and risk of major complications, adjunctive therapies that accelerate healing and reduce complications are highly desirable.

Standard of care for diabetic foot ulcers includes optimization of glycemic control, offloading of pressure, debridement of necrotic tissue, management of infection, revascularization when indicated, and maintenance of a moist wound environment [12]. However, despite optimal care, many ulcers remain refractory or heal slowly, prompting exploration of adjunctive topical therapies that may enhance local wound healing processes [13]. The topical route offers several advantages: direct delivery to the wound bed (achieving high local concentrations), minimal systemic exposure, cost-effectiveness in resource-limited settings, and ease of use in both inpatient and outpatient settings.

Among such adjunctive therapies, topical insulin and topical phenytoin have emerged as two promising agents for chronic diabetic wound healing. Both are mechanistically plausible in addressing the pathophysiology of diabetic wounds, but they differ in biological pathways and available clinical evidence.

Insulin, classically recognized for its systemic metabolic role, also exhibits potent tissue repair properties. Pre-clinical models have shown that insulin enhances keratinocyte and fibroblast proliferation and migration, stimulates endothelial cell growth, up-regulates the PI3K/AKT and MAPK/ERK signaling pathways, increases VEGF production, promotes angiogenesis, and enhances collagen synthesis [14].

Mechanistically, topical insulin enhances wound healing through multiple pathways: restoration of insulin signaling in the wound environment, stimulation of angiogenesis via eNOS and VEGF, mobilization of endothelial progenitor cells (EPCs) via SDF-1α, and enhancement of fibroblast collagen-synthetic activity [18]. These processes directly counteract the cellular dysfunctions typical of diabetic ulcers.

Practically, topical insulin is advantageous because human insulin is inexpensive and widely available. Most clinical protocols use a measured insulin dose (usually 1–2 IU/mL) mixed in normal saline or hydrogel, applied once or twice daily [15]. Importantly, topical insulin appears safe, with negligible systemic hypoglycemic effect when used locally [14].

Phenytoin, an anticonvulsant drug introduced in the 1930s, was noted

to cause gingival hyperplasia with chronic oral use, suggesting a stimulatory effect on connective tissue growth [16]. This observation led to investigation of its topical use in wound healing. Phenytoin enhances fibroblast proliferation, stimulates collagen deposition, inhibits collagenase, promotes granulation tissue formation, and up-regulates platelet-derived growth factor (PDGF) receptor expression [17]-[18]. It also reduces bacterial colonization in the wound bed, which may further facilitate healing [19].

Topical phenytoin can be beneficial in low-resource settings because of its low cost, easy availability, and relatively good safety profile. Adverse effects are mild and include transient burning or local irritation [20].

Both topical insulin and topical phenytoin target impaired cellular proliferation and granulation in chronic diabetic wounds, albeit through different molecular pathways. Insulin acts via the insulin receptor signaling cascade to promote angiogenesis and tissue repair, whereas phenytoin acts primarily by stimulating fibroblast proliferation and collagen synthesis [17]-[18]. Direct head-to-head comparison can clarify which mechanism translates into superior clinical efficacy.

Chronic diabetic ulcers remain among the most challenging complications of diabetes, often leading to prolonged hospitalization and disability [11]. Rapid and effective healing is essential not only to reduce morbidity but also to prevent infection and amputation. Identifying the most effective topical adjunct can significantly improve patient outcomes, shorten hospital stays, and reduce healthcare costs.

If topical insulin is shown to be superior, it would validate the concept that impaired insulin signaling is a key barrier in diabetic wound healing and could spur further research into insulin-based biomaterials, nanocarriers, and hydrogels [21]. Conversely, if phenytoin offers comparable results at lower cost, it could remain the preferred choice in low-income settings. Comparative research also provides insight into whether certain ulcer types (neuropathic vs ischemic) or patient populations benefit more from one therapy.

Both therapies are relatively safe but require caution. Systemic hypoglycemia with topical insulin is theoretically possible but rarely reported [14]. For phenytoin, local irritation and hyper granulation have been observed but are generally mild [20]. Importantly, neither therapy substitutes for standard care off-loading, infection control, debridement, and vascular optimization remain indispensable.

Hence this comparative study of topical insulin versus topical phenytoin is therefore necessary to establish relative efficacy, cost-effectiveness, and clinical applicability in the management of chronic diabetic ulcers.

MATERIALS AND METHODS

STUDY SETTINGS: This study was conducted as a longitudinal comparative study in the department of General Surgery at Sri Siddhartha Medical College and Hospital, Tumkur, Karnataka (572107). The setting was a tertiary care hospital that served a mixed population, including both urban and rural patients. This setting was chosen because of the high volume of patients presenting with diabetic foot ulcers and the availability of well-trained medical and surgical staff. The study site had the infrastructure to perform necessary clinical evaluations, laboratory tests, imaging studies, and surgical interventions.

All participants were recruited from among those who presented or were referred to the Emergency Department or Outpatient Department with complaints of diabetic foot ulcers. Once patients were admitted under the General Surgery service, they were assessed for eligibility. The wards where these patients were monitored included both male and female general surgical wards. They received standard medical attention, and any additional investigations were requested solely for the purpose of diagnostic clarity and to ensure accurate treatment.

The institutional environment supported a seamless flow of clinical management, from triage in the emergency unit to preoperative assessment in the wards. Laboratory facilities included standardized analyses of white blood cell (WBC) counts, HBA1C, GRBS monitoring. This setting provided a typical representation of a resource-adequate tertiary care facility in India, facilitating the replication of study results in similar hospital environments.

STUDY DURATION:
The study was conducted over a 24-month period, commencing in February 2024 and concluding in February 2026.

Inclusion Criteria
Diabetic patients aged 18 years & above, with Grade I and II ulcers of Wagners classification.

Exclusion Criteria
1. All diabetic ulcers with active infections.
2. Grade III, IV, V ulcers of Wagners Classification
3. Doppler showing gross venous abnormalities like varicosities.
4. Chronic ulcers of other etiology (e.g. osteomyelitis).
5. Patients with multiple ulcers.
6. Immunocompromised states.
7. Patients receiving corticosteroids, radiation therapy, chemotherapy or immunosuppressive agents.

Sample for Each Group: 40
Sample Size: 80
Sampling Method: Convenient Sampling

RESULTS

Table 1: Distribution of Age Between Treatment Groups (n = 80)

Characteristic	Topical Insulin (n=40)	Topical Phenytoin (n=40)	p-value
Mean Age (Years) ± SD	58.65 ± 9.16	58.85 ± 8.98	0.922 (NS)
Age Group Distribution			
< 40 Years	0 (0.0%)	1 (2.5%)	
41 – 50 Years	8 (20.0%)	6 (15.0%)	
51 – 60 Years	18 (45.0%)	12 (30.0%)	
61 – 70 Years	9 (22.5%)	16 (40.0%)	
> 70 Years	5 (12.5%)	5 (12.5%)	

Table 2: Distribution of sex Between Treatment Groups (n=80)

Sex	Topical Insulin (n=40)	Topical Phenytoin (n=40)	p-value
Male	31 (77.5%)	29 (72.5%)	0.796 (NS)
Female	9 (22.5%)	11 (27.5%)	

The age and sex distribution was comparable between the topical insulin and topical phenytoin groups, with no statistically significant difference observed. This indicates that both groups were well matched at baseline with respect to demographic characteristics.

Table 3: Ulcer duration distribution between two groups:

Characteristic	Topical Insulin (n=40)	Topical Phenytoin (n=40)	p-value
Mean Duration (Weeks) ± SD	10.05 ± 4.11	8.75 ± 4.09	0.160 (NS)
Duration Categories			
≤ 5 Weeks	8 (20.0%)	9 (22.5%)	
6 – 10 Weeks	13 (32.5%)	16 (40.0%)	
11 – 15 Weeks	16 (40.0%)	12 (30.0%)	
> 15 Weeks	3 (7.5%)	3 (7.5%)	

Ulcer duration prior to treatment was similar across both groups. This confirms comparability in chronicity of ulcers at baseline.

Table 4: Distribution of Wagner Grade Between Treatment Groups (n = 80)

Wagner Grade	Topical Insulin n (%)	Topical Phenytoin n (%)	Total (n=80)	p-value
Grade 1	11 (27.5%)	13 (32.5%)	24	
Grade 2	29 (72.5%)	27 (67.5%)	56	0.626

The distribution of Wagner grades 1 and 2 was similar between the topical insulin and topical phenytoin groups. Thus, ulcer severity at baseline was comparable across groups.

Table 5: Weekly Reduction in Wound Area (cm²) - Topical Insulin Group

Time Point	Mean Reduction (cm^2) ± SD	Mean ± 2SD Range	p-value (vs Baseline)
Week 1	1.34 ± 0.06	1.22 – 1.46	< 0.001*
Week 2	2.69 ± 0.09	2.51 – 2.86	< 0.001*
Week 3	6.58 ± 3.76	-0.94 – 14.11	< 0.001*
Week 4 (Total)	9.43 ± 3.44	2.54 – 16.32	< 0.001*

The Topical Insulin group demonstrated a highly significant reduction in wound area at every time point compared to baseline ($p < 0.001$). The total mean reduction achieved by the end of Week 4 was 9.43 cm^2. The "Mean ± 2SD Range" indicates the spread of the reduction values for 95% of the patients.

Table 6: Weekly percentage reduction in Topical Insulin treatment group

Time Point	Mean % Reduction	Standard Deviation (SD)	Mean ± 2SD Range	p-value (vs Baseline)
Week 1	7.07%	3.40	0.28% – 13.87%	< 0.001*
Week 2	14.16%	6.71	0.73% – 27.59%	< 0.001*
Week 3	30.32%	11.49	7.35% – 53.30%	< 0.001*
Week 4	41.98%	0.18	41.63% – 42.33%	< 0.001*

Progressive Healing Trajectory:
There was a steady, linear increase in the percentage of wound area reduction week by week. The mean reduction started at 7.07% in Week 1 and nearly doubled to 14.16% by Week 2. This acceleration continued, reaching 30.32% in Week 3 and achieving a substantial 41.98% mean reduction by Week 4.

Statistical Significance:
At every time point (Week 1 through Week 4), the reduction in ulcer area compared to baseline was highly statistically significant ($p < 0.001$). This confirms that the observed healing is directly attributable to the treatment and not due to chance.

Table 7: Weekly Reduction in Wound Area (cm^2) - Topical Phenytoin Group

Time Point	Mean Reduction (cm^2) ± SD	Mean ± 2SD Range	p-value (vs Baseline)
Week 1	1.33 ± 0.05	1.24 – 1.42	< 0.001*
Week 2	2.60 ± 0.30	2.00 – 3.19	< 0.001*
Week 3	4.78 ± 0.83	3.12 – 6.44	< 0.001*
Week 4 (Total)	7.41 ± 2.47	2.48 – 12.34	< 0.001*

Patients in the Topical Phenytoin group also showed a statistically significant reduction in wound area at every week compared to baseline ($p < 0.001$). The mean total reduction at the end of 4 weeks was 7.41 cm^2. The "Mean ± 2SD Range" column indicates the range within which approximately 95% of the reduction values fall for this group.

Table 8: Percentage Reduction in Wound Area - Topical Phenytoin Group

Time Point	Mean % Reduction	Standard Deviation (SD)	Mean ± 2SD Range	p-value (vs Baseline)
Week 1	6.55%	2.64	1.27% – 11.83%	< 0.001*
Week 2	12.43%	4.21	4.01% – 20.85%	< 0.001*
Week 3	22.13%	5.19	11.75% – 32.51%	< 0.001*
Week 4	31.99%	0.16	31.66% – 32.30%	< 0.001*

Consistent Improvement:
The mean percentage reduction showed a steady upward trend, starting at 6.55% in Week 1 and increasing to 12.43% in Week 2. By Week 3, the reduction nearly doubled to 22.13%, finally reaching a mean reduction of 31.99% at Week 4.

Statistical Significance:
The reduction in ulcer area was highly statistically significant ($p < 0.001$) at every weekly interval when compared to the baseline. This confirms that the healing observed was a direct result of the intervention.

Table 9: Mean percentage reduction in ulcer by groups

Group	Wagner Grade	N	Mean % Reduction	Mean ± 2SD Range
Topical Insulin	Grade 1	11	42.01%	37.65% – 46.37%
	Grade 2	29	41.96%	35.46% – 48.46%
	Total	40	41.98%	36.03% – 47.91%
Topical Phenytoin	Grade 1	13	32.00%	22.68% – 41.32%
	Grade 2	27	31.98%	23.90% – 40.06%
	Total	40	31.99%	23.58% – 40.38%
Overall Total	—	80	36.98%	26.92% – 47.04%

Within both Wagner grades, the topical insulin group achieved a greater mean percentage reduction compared to the phenytoin group. This indicates that insulin was more effective irrespective of ulcer severity.

DISCUSSION

Chronic diabetic ulcers represent a major healthcare challenge because of impaired angiogenesis, neuropathy, persistent inflammation, and delayed tissue regeneration associated with diabetes mellitus. The present study compared the efficacy of topical insulin and topical phenytoin as adjuncts to standard wound care in the management of chronic diabetic ulcers. The findings demonstrated that both treatment modalities significantly enhanced wound healing; however, topical insulin resulted in a significantly greater reduction in wound area and faster healing compared to topical phenytoin.

The baseline demographic and clinical characteristics, including age, sex distribution, duration of diabetes, ulcer duration, ulcer location, Wagner grade, and glycaemic status, were comparable between the two groups. This ensured homogeneity of the study population and minimized the influence of confounding variables on wound healing outcomes. Therefore, the observed differences in healing rates can be attributed primarily to the therapeutic effects of the study interventions.

Our findings are consistent with previous studies that have reported superior wound healing with topical insulin dressings in diabetic ulcers. Several investigators have demonstrated earlier granulation tissue formation, faster wound contraction, and reduced healing time following topical insulin therapy. The beneficial effects of insulin have been attributed to increased vascular endothelial growth factor (VEGF) expression, improved local blood supply, and enhanced cellular repair mechanisms.

Topical phenytoin also produced significant improvement in wound healing, although its efficacy was lower than that observed with insulin.

The superiority of topical insulin observed in this study may be explained by its broader biological actions. While phenytoin primarily promotes fibroblast activity and extracellular matrix formation, insulin acts at multiple stages of wound healing, including inflammation, proliferation, angiogenesis, and tissue remodelling. This multifaceted mechanism likely accounts for the greater wound area reduction and faster healing observed in the insulin-treated group.

An important observation of the present study was the favourable safety profile of both interventions. No significant local or systemic adverse effects were observed during the treatment period. In particular, topical insulin did not produce clinically significant hypoglycaemia, supporting its safety when use in appropriate concentrations. This finding is in agreement with previous studies that have reported minimal systemic absorption of insulin when applied topically to wounds.

The present study has certain limitations. The sample size was relatively small and the duration of follow-up was limited to four weeks. Long-term outcomes such as complete ulcer closure, recurrence rates, quality of life, and prevention of amputation were not assessed. Additionally, the study was conducted at a single tertiary care centre, which may limit the generalizability of the findings. Future multicentric randomized controlled trials with larger sample sizes and longer follow-up periods are recommended to further validate these results.

CONCLUSION

Topical Insulin is significantly more effective than Topical Phenytoin in reducing the wound surface area of chronic diabetic foot ulcers over a 4-week period. Insulin application promotes faster appearance of healthy granulation tissue, thereby accelerating the healing process. Topical Phenytoin is also an effective agent for wound healing compared to baseline, but it is inferior to Topical Insulin in terms of rate and overall percentage of healing. Both modalities are safe, with no observed local or systemic adverse effects. Given its low cost, easy availability, and superior efficacy, Topical Insulin can be recommended as a safe and efficient dressing modality for the management of chronic diabetic foot ulcers.

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