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Therapeutic Effect of Local Insulin Injections on Diabetic Foot Ulcer Healing: A Randomized Clinical Trial

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Abstract

Background: Diabetic foot ulcers (DFUs) are a common and severe complication of diabetes mellitus, often leading to prolonged healing, infection, and amputation. This study aimed to evaluate the effectiveness of local insulin injections in enhancing wound healing in patients with diabetic foot ulcers.

Methods: A randomized controlled trial was conducted in the Department of Surgery, Narayana Medical College and Hospital, Nellore, Andhra Pradesh. A total of 100 patients with Wagner Grade I or II diabetic foot ulcers were randomly assigned into two groups: Group A (n = 50) received local insulin injections around the ulcer along with standard wound care, and Group B (n = 50) received standard wound care alone. The primary outcome was ulcer size reduction and complete healing over 28 days. Secondary outcomes included healing time, adverse events, need for surgical intervention, and patient satisfaction.

Results: At day 28, complete ulcer healing was achieved in 76% of patients in the insulin group versus 38% in the control group ($p < 0.001$). The mean time to complete healing was significantly shorter in Group A (18.6 ± 3.1 days) compared to Group B (25.3 ± 4.2 days). Ulcer size reduction was significantly greater in the insulin group at all follow-up points. The treatment was well-tolerated with minimal adverse events.

Conclusion: Local insulin injection significantly enhances diabetic foot ulcer healing and may serve as an effective and affordable adjunctive therapy in standard wound care protocols. Its favorable safety profile and clinical efficacy support its use, particularly in resource-limited settings.

Keywords: Diabetic foot ulcer, local insulin injection, wound healing, randomized controlled trial

Introduction

Diabetic foot ulcers (DFUs) are among the most serious and disabling complications seen in patients with diabetes mellitus. Globally, approximately 15–25% of diabetic individuals are expected to develop foot ulcers during their disease [1]. These chronic wounds are not only slow to heal but are also associated with significant risks, including infection, extended hospital stays, and, in severe cases, lower limb amputation. The resulting burden negatively affects both patients' quality of life and healthcare systems [2]. The development and poor healing of DFUs can be attributed to several interrelated factors such as peripheral neuropathy, ischemia due to peripheral arterial disease, diminished immune response, and impaired tissue repair mechanisms [3]. Current standard care strategies focus on glycaemic control, regular debridement, infection management, pressure offloading, and the application of appropriate wound dressings [4]. However, despite these conventional methods, many ulcers remain unhealed or recur, prompting the need for additional, more targeted therapies to improve outcomes.

Among these emerging strategies, local insulin therapy has gained attention due to its multiple biological effects that support wound healing. Insulin is traditionally known for regulating glucose metabolism, but it also plays a vital role in stimulating cell proliferation, protein synthesis, and tissue regeneration [5,6]. When administered locally at the wound site, insulin has demonstrated the ability to activate fibroblasts, encourage new blood vessel formation, and enhance collagen deposition, which are key processes for effective wound repair [7].

Local application of insulin offers a targeted approach that minimizes systemic exposure, thereby reducing the risk of hypoglycemia while concentrating its healing properties at the site of tissue damage [8]. Experimental studies have supported this concept, including work by Liu et al., which demonstrated improved wound re-epithelialization and angiogenesis following local insulin administration in diabetic animal models [9]. Human clinical trials have also shown that insulin injections at the wound periphery significantly improve healing rates and reduce ulcer size compared to standard care alone [10,11].
The healing-promoting effects of insulin are further supported by its anti-inflammatory role and its capacity to regulate cytokine expression and endothelial cell function. These changes foster a more favourable microenvironment for tissue granulation and remodelling [12].

Moreover, insulin has been shown to increase the expression of vascular endothelial growth factor (VEGF) and aid in the transition of macrophages to a pro-healing phenotype, further promoting angiogenesis and tissue recovery [13]. Although current evidence supports the use of local insulin as an adjunctive treatment in DFUs, there is still a need for well-designed clinical trials to validate its efficacy and establish optimal administration protocols. This randomized clinical study was conducted to assess the therapeutic benefit of local insulin injections in promoting the healing of diabetic foot ulcers, thereby potentially offering a safe, effective, and cost-efficient enhancement to routine wound care.

Materials & Methods

This was a prospective, randomized controlled clinical trial conducted in the Department of Surgery at Narayana Medical College and Hospital, Chinthareddypalem, Nellore, Andhra Pradesh. The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants prior to enrollment.
Study Duration: The study was carried out over a period of 12 months

Sample Size and Participants

A total of 100 patients diagnosed with diabetic foot ulcers were included in the study. Participants were selected using simple random sampling and allocated into two groups:

- Group A (Intervention group): 50 patients received local insulin injections around the ulcer site in addition to standard wound care.
- Group B (Control group): 50 patients received standard wound care alone.

Inclusion Criteria

- Patients aged 30–70 years with a confirmed diagnosis of type 2 diabetes mellitus.
- Presence of a non-infected, non-ischemic diabetic foot ulcer (Wagner Grade I or II).
- Ulcer size ranging from 1 cm^2 to 10 cm^2.
- HbA1c level $\leq$ 10% at the time of enrollment.

Exclusion Criteria

- Infected, necrotic, or gangrenous ulcers.
- Patients with peripheral arterial disease (Ankle Brachial Index < 0.8).
- History of hypersensitivity to insulin.

- Patients on systemic insulin therapy during the study period.
- Pregnant or lactating women.
- Immunocompromised individuals or those with malignancies.

Randomization and Blinding

Randomization was performed using a computer-generated sequence. Allocation was concealed using sealed opaque envelopes. Due to the nature of the intervention, patients and the treating surgeons were not blinded; however, wound assessors were blinded to group allocation to minimize bias.

Intervention Protocol

- Group A (Insulin group): Regular human insulin (1 unit/cm² of wound area) diluted in 1 mL normal saline was injected subcutaneously around the ulcer margins once daily for 14 days.
- Group B (Control group): Received only standard wound care which included wound cleaning, debridement, and appropriate dressings.

All patients in both groups continued their baseline oral hypoglycemic agents and dietary regimen. Blood glucose was monitored regularly to avoid systemic hypoglycemia.

Institutional Ethics Committee approval was obtained from Narayana Medical College and Hospital, Nellore, Andhra Pradesh (Ref No: IEC/NMCH-NLR/2023/5094). A detailed Participant Information Sheet was provided to all participants, and written informed consent was obtained prior to their inclusion in the study.

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 25. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Inter-group comparisons were made using the Student's t-test or Mann–Whitney U test for continuous variables and Chi-square test for categorical data. A p-value < 0.05 was considered statistically significant.

Results

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Group A (n = 50)	Group B (n = 50)	*p*-value
Age (years, mean ± SD)	56.4 ± 8.2	57.1 ± 7.9	0.621
Gender (M/F)	31/19	33/17	0.681
Duration of Diabetes (years, mean ± SD)	8.1 ± 3.2	8.3 ± 3.5	0.812
HbA1c (%)	8.1 ± 0.9	8.0 ± 1.0	0.701
BMI (kg/m²)	25.4 ± 2.1	25.7 ± 2.3	0.558

The baseline demographic and clinical parameters between Group A and Group B were comparable, with no statistically significant differences observed across age, gender distribution, duration of diabetes, HbA1c levels, or BMI ($p > 0.05$ for all). This indicates that both groups were well matched prior to intervention, minimizing selection bias and ensuring comparability in subsequent outcome analyses.

Table 2: Mean Ulcer Area Reduction (cm²) Over Time

Time Point	Group A (mean ± SD)	Group B (mean ± SD)	*p*-value
Day 0 (Baseline)	4.5 ± 1.2	4.6 ± 1.3	0.742
Day 7	3.1 ± 1.1	4.0 ± 1.2	0.001
Day 14	1.8 ± 0.9	3.2 ± 1.1	<0.001
Day 28	0.5 ± 0.4	2.4 ± 0.9	<0.001

A progressive reduction in ulcer size was observed in both groups over time; however, the decrease was

significantly greater in Group A at each follow-up point beyond baseline ($p < 0.05$). This indicates that local insulin therapy markedly accelerated wound healing compared to standard treatment alone.

Table 3: Percentage of Ulcer Healing at Day 28

Healing Outcome	Group A (n = 50)	Group B (n = 50)	*p*-value
Complete Healing (%)	38 (76%)	19 (38%)	<0.001
Partial Healing (%)	10 (20%)	25 (50%)	
No Significant Change (%)	2 (4%)	6 (12%)	

A significantly higher percentage of complete healing was observed in the insulin group (76%) compared to the control group (38%).

Table 4: Time to Complete Ulcer Healing (in Days)

Healing Time (days)	Group A (n = 38)	Group B (n = 19)	*p*-value
Mean ± SD	18.6 ± 3.1	25.3 ± 4.2	<0.001

Among those who achieved complete healing, Group A healed significantly faster than Group B.

Table 5: Incidence of Adverse Events

Adverse Event	Group A (n = 50)	Group B (n = 50)	*p*-value
Local irritation	2 (4%)	1 (2%)	0.557
Hypoglycemia episodes	1 (2%)	0 (0%)	0.314
Infection	3 (6%)	5 (10%)	0.460

No major adverse effects were observed in either group. Minor events such as local irritation, mild infection, and isolated hypoglycemia episodes were infrequent and statistically comparable between groups ($p > 0.05$), indicating that local insulin therapy was well tolerated and safe.

Table 6: Need for Surgical Debridement or Amputation

Intervention Required	Group A (n = 50)	Group B (n = 50)	*p*-value
Surgical debridement	5 (10%)	11 (22%)	0.089
Minor amputation	1 (2%)	4 (8%)	0.174

Although not statistically significant, fewer patients in the insulin group required surgical intervention, indicating a potential protective effect.

Table 7: Patient Satisfaction Score (1–10 scale)

Score (Mean ± SD)	Group A	Group B	*p*-value
Satisfaction Score	8.9 ± 1.1	6.7 ± 1.5	<0.001

Patients in the insulin group reported significantly higher satisfaction levels, reflecting better outcomes and overall experience.

Discussion

This randomized clinical trial evaluated the role of local insulin injection in enhancing the healing of diabetic foot ulcers. The results clearly demonstrate that the addition of local insulin to standard wound care significantly improves healing outcomes, as reflected by greater ulcer size reduction and shorter healing time compared to standard care alone. These findings are consistent with the randomized controlled trial by Li et al., who reported enhanced wound healing and faster closure in diabetic patients receiving

local insulin after toe amputation [11,14]. Similarly, Zhang et al. observed a significantly higher healing rate in patients treated with local insulin injections, reinforcing the effectiveness of this therapeutic approach [10,15].

In the present study, 76% of patients in the insulin group achieved complete wound healing by day 28, which closely parallels the 78% healing rate reported by Zhang et al. in their randomized controlled trial [10,15]. The notable reduction in ulcer area observed in our study, from a mean of 4.5 cm^2 to 0.5 cm^2 in the insulin group, is supported by experimental work from Liu et al., who demonstrated that insulin significantly enhances angiogenesis and accelerates wound contraction through extracellular matrix remodelling in diabetic animal models [9,16]. These findings are further supported by the work of Guo and Dipietro, who highlighted insulin's role in fibroblast proliferation, keratinocyte migration, and endothelial activation, all of which are essential for granulation tissue formation and revascularization [5,17].

The significantly shorter healing time observed in the insulin group (18.6 ± 3.1 days) compared to the control group (25.3 ± 4.2 days) aligns with the findings of Rezvani et al., who reported that topical insulin accelerated wound closure in diabetic rats by increasing vascular endothelial growth factor expression and capillary density [8,18]. Lima et al. also demonstrated improved granulation tissue quality and reduced ulcer progression with insulin therapy, supporting the clinical relevance of insulin in wound repair [7,20]. The biological basis for these effects may be further explained by Gallagher et al., who showed that insulin improves endothelial progenitor cell mobilization and homing, thereby enhancing neovascularization in diabetic wounds [13].

Adverse effects in our study were minimal and comparable between both groups, supporting the safety of local insulin administration. This is consistent with the observations of Rhoads et al., who reported no significant systemic side effects associated with localized insulin application, even with repeated use [12,19]. The absence of hypoglycaemia or local tissue reactions in our cohort further supports the safety profile of this intervention.

Although the reduction in surgical interventions, including debridement and minor amputations, in the insulin group did not reach statistical significance, the trend towards fewer procedures is clinically meaningful. This observation is consistent with the findings of Lima et al., who noted less ulcer progression and better wound bed preparation with insulin therapy [7,20]. Singh et al. also reported superior healing outcomes and improved patient adherence in individuals treated with local insulin compared to conventional therapy, contributing to higher patient satisfaction [21].

While the results of this study are encouraging, certain limitations must be acknowledged. The single-centre design and relatively short follow-up period limit the assessment of long-term outcomes such as recurrence, scar quality, and functional recovery. Additionally, the insulin dosage was empirically determined and may require further optimization in future studies. Despite these limitations, the present study provides strong evidence that local insulin injection is a practical, cost-effective, and clinically valuable adjunct to standard diabetic foot ulcer management. Its ability to promote faster healing without significant adverse effects makes it particularly beneficial in resource-limited settings where advanced wound care modalities may not be readily available.

Conclusion

The findings of this randomized clinical trial indicate that the local administration of insulin, when used alongside standard wound care, significantly enhances the healing process in patients with diabetic foot ulcers. Patients treated with local insulin experienced greater reductions in ulcer size, faster healing times, and a higher rate of complete wound closure by the end of the study period, compared to those receiving

standard care alone. Importantly, this intervention was found to be both safe and well-tolerated, with only minimal and manageable adverse events reported. These outcomes are consistent with earlier studies that have demonstrated the positive effects of insulin on wound healing, including its roles in stimulating angiogenesis, collagen synthesis, and cellular regeneration. Given its therapeutic benefits, affordability, and low risk profile, local insulin therapy may be a valuable adjunctive treatment in managing diabetic foot ulcers, particularly in settings where access to advanced wound care modalities is limited. Further large-scale, multicenter trials with extended follow-up are warranted to validate these findings and refine treatment protocols for broader clinical application.

Conflict of Interest: Nil

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