International Surgery Journal
Baid S et al. Int Surg J. 2025 Sep;12(9):1492-1496
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20252681

Original Research Article

Efficacy of topical insulin versus normal saline in promoting granulation tissue formation and healing in diabetic foot ulcers: a prospective non-randomized interventional comparative study

Saloni Baid[1], Raj Kumar Sharma[1], Mukul Sharma[1], Sachin Sharma[2]*

[1]Department of Surgery, Dr RPGMC Kangra at Tanda, Himachal Pradesh, India
[2]Department of Pharmacology, Dr RPGMC Kangra at Tanda, Himachal Pradesh, India

Received: 15 July 2025
Accepted: 19 August 2025

***Correspondence:**
Dr. Sachin Sharma,
E-mail: s1984kaka@gmail.com

ABSTRACT

Background: Diabetic foot ulcers (DFUs) represent a severe complication of diabetes mellitus, substantially increasing the risk of morbidity, extended hospital stays and potential limb amputation. Conventional management strategies often yield suboptimal healing outcomes, necessitating exploration of novel therapies. Topical insulin has emerged as a potential adjunct due to its mitogenic, angiogenic and anti-inflammatory properties. To evaluate the efficacy of topical insulin versus normal saline in promoting granulation tissue formation and wound healing in patients with diabetic foot ulcers.

Methods: A prospective, non-randomized interventional comparative study was conducted at Dr. R.P.G.M.C. Kangra at Tanda over one year, enrolling 40 patients with Wagner grade I–II DFUs. Patients were allocated into two groups: Group A (Topical Insulin) received dressings with 30 IU regular human insulin in 30 ml normal saline, while Group B (Control) received normal saline dressings alone. Granulation tissue percentage, ulcer area and fasting blood sugar (FBS) levels were assessed at baseline, 1 week and 3 weeks.

Results: Significant improvements in fasting blood sugar (FBS) levels and ulcer area were observed within both groups. However, Group A exhibited a significantly greater increase in granulation tissue formation (from 21.44% to 73.74%) compared to Group B (from 17.46% to 56.6%) at 3 weeks ($p<0.05$). No significant inter-group difference was observed in ulcer area reduction within the study duration.

Conclusions: Topical insulin significantly enhances granulation tissue formation in DFUs and represents a safe, cost-effective adjunct to conventional therapy, particularly beneficial in resource-limited settings.

Keywords: Diabetic foot ulcer, Granulation tissue, Normal saline, Topical insulin, Wound healing

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action or both. It represents a significant global health challenge, with an estimated 537 million adults affected worldwide in 2021, a number projected to rise to 643 million by 2030 and 783 million by 2045, as projected by the International Diabetes Federation (IDF).[1] Among the various complications associated with diabetes, diabetic foot ulcers (DFUs) remain one of the most serious and debilitating, contributing to substantial morbidity, prolonged hospitalization and a considerable socioeconomic burden.[2] Diabetic foot ulcers are defined as non-healing or chronic wounds located below the ankle in individuals with diabetes. Individuals with diabetes have an estimated lifetime risk of 15–25% for developing a foot ulcer.[3] The pathogenesis of DFUs is multifactorial, involving peripheral neuropathy, peripheral arterial disease and a compromised immune response, all of which impede wound healing and

predispose to infection.[4] If inadequately managed, DFUs can lead to severe complications, including osteomyelitis and lower limb amputation, with up to 85% of diabetes-related amputations being preceded by a foot ulcer.[5] Wound healing in diabetic individuals is a complex and prolonged process due to impaired angiogenesis, delayed granulation tissue formation and dysfunctional fibroblast activity, ultimately resulting in poor tissue repair and regeneration.[6] The formation of granulation tissue is an essential phase in the wound healing process, providing the groundwork for epithelialization and subsequent tissue repair. Optimizing granulation tissue formation is, therefore, pivotal in improving outcomes for patients with DFUs.[7] Conventional management of DFUs typically involves systemic glycemic control, wound debridement, infection control, offloading and moist wound care using agents such as normal saline. However, despite these measures, healing rates remain suboptimal, necessitating the exploration of novel therapeutic approaches to enhance tissue regeneration.[8] In recent years, topical application of insulin has emerged as a promising modality in wound management. Insulin plays a vital role in cellular metabolism, protein synthesis and tissue repair and possesses anti-inflammatory, angiogenic and mitogenic properties that can accelerate wound healing when applied locally.[9]

Several experimental and clinical studies have demonstrated the beneficial effects of topical insulin in promoting wound healing by enhancing fibroblast proliferation, collagen deposition and neovascularization, thereby facilitating faster granulation tissue formation and re-epithelialization.[10,11] Despite these promising outcomes, the clinical evidence comparing topical insulin with conventional agents such as normal saline in the management of diabetic foot ulcers remains limited. In this context, the present study was undertaken to evaluate the efficacy of topical insulin versus normal saline in promoting granulation tissue formation and wound healing in patients with diabetic foot ulcers. By comparing these two interventions in a prospective non-randomized interventional setting, this study aims to contribute valuable clinical evidence to optimize the management strategies for diabetic foot ulcers.

METHODS

Study design

This study followed a prospective, non-randomized, interventional and comparative design.

Study setting

The research was conducted in the Department of Surgery at Dr. Rajendra Prasad Government Medical College (R.P.G.M.C.), Kangra at Tanda, a multispecialty tertiary care center situated in the Kangra Valley of Himachal Pradesh, India.

Study duration

The study was conducted for a period of one year, from May 2024 to April 2025.

Sample size

A total of 40 patients, clinically diagnosed with diabetic foot ulcers (DFU) and admitted to the surgical wards were enrolled.

Inclusion criteria

Patients consenting to be part of study. Patients aged above 20 years and having DFU with grade I and II ulcers as per Wagner's classification. Absence of severe systemic illnesses. No significant granulation tissue formation at presentation.

Exclusion criteria

Patients with grossly infected, non-sterile wounds. Grade III to V DFU (Wagner's classification). Patients over 70 years, immunocompromised individuals, pregnant women, those with hepatic or renal disease, osteomyelitis or uncontrolled diabetes (HbA1c>8%). And patient refuse to participate.

Study procedure

The study population was selected as per inclusion and exclusion criteria from department of Surgery at Dr. RPGMC Tanda. A thorough clinical assessment was performed and documented. Relevant investigation like laboratory and X-ray of foot was done. The eligible patients were divided into two groups A and B based on odd and even numbers respectively. Group A (Topical Insulin) received dressings prepared by mixing 30 IU of regular human insulin in 30 ml of normal saline, while Group B (Control) was treated with conventional dressings using normal saline alone. The ulcer area (measured in cm^2) and percentage of granulation tissue formation were recorded at baseline (Day 0), after 1 week and at 3 weeks of treatment. Additionally, fasting blood sugar (FBS) levels were monitored at the same intervals to assess glycemic control.

Statistical analysis

The data was collected, cleaned and entered using Microsoft Excel spreadsheet; and was analyzed in Statistical Package for Social Science (SPSS) v 27 to draw relevant conclusions. Qualitative data will be expressed in terms of percentages and proportions. Quantitative data will be expressed in terms of Mean and Standard deviation. Association between two qualitative variables will be seen by using Chi square test, ANOVA and Post Hoc Tukey test. A p value of <0.05 will be considered as statistically significant whereas a p value <0.001 will be considered as highly significant.

RESULTS

A total of 40 patients were included in the study and allocated into two groups: Group A (assigned odd serial numbers) and Group B (assigned even serial numbers). Group A (Topical Insulin) was treated with dressings prepared by combining 30 IU of regular human insulin with 30 ml of normal saline, whereas Group B (Control) received conventional dressings using normal saline alone.

The average age of participants in Group A (topical insulin) was 49.8±12.64 years, compared to 57.1±9.29 years in Group B (normal saline), with the difference being statistically significant (p=0.034). The male-to-female ratio was 23:17 (57.5% male, 42.5% female), with no significant gender distribution difference between the groups (p=0.056). The mean fasting blood sugar (FBS) levels showed a gradual decline throughout the study period in both groups. In Group A, FBS reduced from 153.35 mg/dl at baseline to 123.6 mg/dl at 3 weeks. In Group B, FBS reduced from 141.65 mg/dl to 123.45 mg/dl over the same period. The decrease was statistically significant within each group (p<0.05), but comparable between groups at 1 and 3 weeks (p>0.05).

At the beginning of the study, the mean ulcer area measured 19.45±5.98 cm² in Group A and 18.05±6.02 cm² in Group B, with no statistically significant difference between them (p=0.216). After one week of treatment, the mean ulcer area decreased to 18.95±5.35 cm² in Group A and 17.80±5.51 cm² in Group B, which also did not reach statistical significance (p=0.310). By the end of three weeks, both groups showed further reductions in ulcer size, with Group A reporting a mean area of 13.81±4.72 cm² and Group B 13.10±5.01 cm². Again, this difference was not statistically significant (p=0.289) as shown in Table 1 and Figure 1. A significant increase in granulation tissue was observed in both groups during the treatment period. At Day 0, the mean percentage granulation was 21.44±5.50% in Group A and 17.46±4.80% in Group B. The difference was found to be statistically significant (t=1.881, p=0.029).

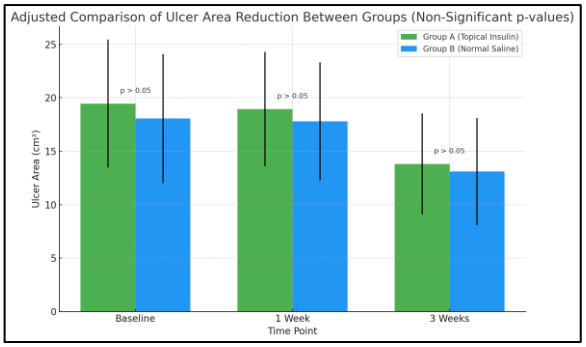

Figure 1: Comparison of mean area of ulcer (sq cm) in both the groups at different time intervals.

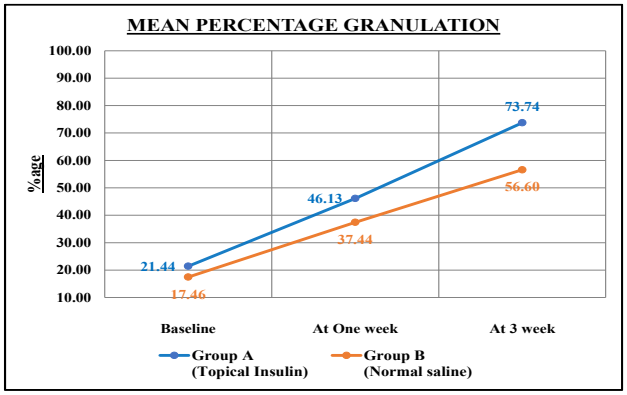

Figure 2: Comparison mean value of percentage granulation in both the groups at different time intervals.

After one week, the mean granulation percentage increased to 46.13±9.20% in Group A and 37.44±8.70% in Group B. The difference at this time point remained statistically significant (t=2.011, p=0.031). By three weeks, further increase in granulation tissue formation was observed in both groups. The average percentage of granulation tissue formation was 73.74±11.00% in Group A, compared to 56.60±12.50% in Group B. This difference was also statistically significant (t=2.199, p=0.045) as shown in Table 2 and Figure 2.

Table 1: Comparison of mean area of ulcer (sq cm) in both the groups at different time intervals.

Variables	Time	Group A (topical insulin)		Group B (normal saline)		P value
		Mean	SD	Mean	SD	
Mean area of ulcer (sq cm)	Baseline	19.45	5.98	18.05	6.02	0.216
	At one week	18.95	5.35	17.80	5.51	0.310
	At 3 weeks	13.81	4.72	13.10	5.01	0.289

Table 2: Comparison of mean percentage granulation in both the groups at different time intervals.

Variables	Time	Group A (topical insulin)		Group B (normal saline)		P value
		Mean	SD	Mean	SD	
Mean percentage granulation	Baseline	21.44	5.50	17.46	4.80	0.029
	At one week	46.13	9.20	37.44	8.70	0.031
	At 3 weeks	73.74	11.00	56.60	12.50	0.045

DISCUSSION

DFUs represent a significant clinical and public health burden, being one of the most serious and disabling complications of diabetes mellitus. Globally, the prevalence of diabetes is rising at an alarming rate, with the International Diabetes Federation estimating 537 million affected adults in 2021, a figure projected to escalate to 783 million by 2045.[1] DFUs account for substantial morbidity, increased healthcare costs, prolonged hospitalizations and are a leading cause of non-traumatic lower limb amputations, with over 85% of such amputations preceded by an ulcer.[12] The complex pathophysiology of DFUs, involving peripheral neuropathy, peripheral arterial disease, impaired angiogenesis and a compromised immune response, contributes to delayed wound healing, reduced granulation tissue formation and an elevated risk of infection.[13] Optimizing wound healing strategies is therefore paramount in mitigating the complications associated with DFUs.

The present prospective, non-randomized interventional comparative study aimed to assess the efficacy of topical insulin versus normal saline in promoting granulation tissue formation and healing in patients with diabetic foot ulcers. The study demonstrated that topical insulin application significantly enhanced granulation tissue formation compared to conventional saline dressings over a three-week period. At baseline, the demographic profile of both groups was comparable in terms of gender distribution. The mean age difference, though statistically significant ($p=0.034$), was unlikely to have confounded the primary outcome, as both groups were within the high-risk middle-aged to elderly demographic typically associated with DFUs.[4]

Both groups exhibited significant intra-group reductions in fasting blood sugar (FBS) levels over the study period, affirming the importance of systemic glycemic control in wound healing. However, inter-group FBS differences at corresponding time intervals were not statistically significant, suggesting that the observed differences in wound healing outcomes were attributable to the local effects of topical insulin rather than variations in glycemic control.

A noteworthy finding of this study was the significant enhancement in granulation tissue formation in the topical insulin group. The percentage of granulation tissue increased from 21.44% at baseline to 73.74% at 3 weeks in Group A, compared to a rise from 17.46% to 56.6% in Group B. The between-group differences were statistically significant ($p<0.05$), corroborating findings from earlier studies that have documented the beneficial effects of topical insulin in wound management.[14,15] Insulin exerts multiple biological effects that favor wound repair. It promotes fibroblast proliferation, collagen synthesis and angiogenesis, while concurrently possessing anti-inflammatory and mitogenic properties.[16] Additionally, insulin enhances endothelial cell function and stimulates vascular endothelial growth factor (VEGF) expression, thereby facilitating neovascularization critical for granulation tissue development.[17]

Studies by Rezvani et al and Lima et al demonstrated accelerated wound healing and increased granulation tissue formation with topical insulin in both experimental and clinical settings.[14,15] The present study's findings are consistent with these reports, reaffirming the role of topical insulin as a viable adjunct in DFU management. While both groups exhibited progressive reductions in ulcer area over the study period, the inter-group differences in ulcer size reduction were not statistically significant at 3 weeks. This suggests that while topical insulin primarily accelerates granulation tissue formation, the actual reduction in wound size may require a longer duration to manifest appreciable between-group differences, as wound contraction and epithelialization generally occur at later stages of healing.[6] Similar observations were reported by Martins et al, who noted faster granulation tissue development with topical insulin without immediate differences in wound size reduction.[18]

The findings of this study underscore the clinical utility of topical insulin as a safe, cost-effective and easily administrable intervention to promote granulation tissue formation in DFUs. Its integration into routine wound care protocols, especially in resource-limited settings, could potentially enhance healing outcomes, reduce hospitalization duration and lower the risk of amputation. Moreover, given its localized action with minimal systemic absorption, topical insulin poses negligible risk of hypoglycemia, as affirmed by the stable glycemic profiles observed in the present study.[19] Nonetheless, careful monitoring remains prudent.

This study had certain limitations. The relatively small sample size and short follow-up duration may limit the generalizability of the results. Additionally, the non-randomized design introduces a potential for selection bias, although baseline characteristics were largely comparable. Future larger-scale, randomized controlled trials with extended follow-up periods are warranted to validate these findings, assess long-term outcomes and establish standardized protocols for topical insulin application.

Further research is also needed to explore optimal dosing, application frequency and possible synergistic combinations with other wound-healing agents such as growth factors and advanced dressings.

CONCLUSION

The present prospective, non-randomized interventional comparative study demonstrated that topical insulin is significantly more effective than conventional normal saline dressings in promoting granulation tissue formation in patients with diabetic foot ulcers. Over a

three-week period, patients receiving topical insulin dressings showed a markedly greater increase in granulation tissue percentage compared to those managed with normal saline alone, while both groups achieved comparable glycemic control and progressive ulcer area reduction. These findings reaffirm the potential of topical insulin as a safe, cost-effective and easily administrable adjunct in the management of diabetic foot ulcers, particularly valuable in resource-constrained settings. Although no significant difference in ulcer size reduction was observed within the study duration, the accelerated granulation response with topical insulin suggests a likely positive impact on overall wound healing if treatment is continued.

However, the study's limitations, including its small sample size, short follow-up period and non-randomized design, necessitate caution in generalizing the results. Larger, randomized controlled trials with longer follow-up and standardized insulin application protocols are warranted to substantiate these findings and better define the role of topical insulin in diabetic wound care algorithms. Integrating such evidence-based, locally acting therapies may help mitigate the substantial morbidity and healthcare burden associated with diabetic foot ulcers.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021. Available from: https://diabetesatlas.org. Accessed on 21 March 2025.
2. Zhang P, Lu J, Jing Y, Tang S, Zhu D, Bi Y. Global epidemiology of diabetic foot ulceration: a systematic review and meta-analysis. Ann Med. 2017;17;49(2):106-16.
3. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293(2):217-28.
4. Armstrong DG, Boulton AJ, Bus SA. Diabetic foot ulcers and their recurrence. New England J Med. 2017;376(24):2367-75.
5. Zhang Y, Lazzarini PA, McPhail SM, van Netten JJ, Armstrong DG, Pacella RE. Global disability burdens of diabetes-related lower-extremity complications in 1990 and 2016. Diabetes Care. 2020;1;43(5):964-74.
6. Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. J Clin Invest. 2007;117(5):1219-22.
7. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet. 2005;12;366(9498):1736-43.
8. Game F, Jeffcoate W. How to assess the quality of clinical trials for diabetic foot ulcer therapies. Foot Diabetes. 2020;24:225-34.
9. Liu Y, Petreaca M, Martins-Green M. Cell and molecular mechanisms of insulin-induced angiogenesis. J Cell Mol Med. 2009;13(12):4492-504.
10. Rezvani O, Kamrani RS, Mobayen MR, Araghi A, Golchi F. Topical insulin as a novel treatment in wound healing in the animal model: a randomized controlled trial. World J Plast Surg. 2019;8(2):200–6.
11. Tiwari VK, Mishra B, Yadav PK, Rastogi A, Gupta SK. Effect of topical application of insulin on wound healing. J Wound Care. 2012;21(12):577–83.
12. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005;366(9498):1719-24.
13. Edmonds M, Foster A. The use of antibiotics in the diabetic foot. The American journal of surgery. 2004;1;187(5): S25-8.
14. Wang J, Xu J. Effects of topical insulin on wound healing: a review of animal and human evidences. Diabetes, metabolic syndrome and obesity. 2020;13:719-27.
15. Lima MH, Caricilli AM, de Abreu LL, Araujo EP, Pelegrinelli FF, Thirone AC, et al. Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: a double-blind placebo-controlled clinical trial. PloS one. 2012;7(5):36974.
16. Greenhalgh DG. Wound healing and diabetes mellitus. Clinics in plastic surgery. 2003;30(1):37-45.
17. Werdin F, Tenenhaus M, Rennekampff HO. Chronic wound care. Lancet. 2008;372(9653):1860-2.
18. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, Ribeiro M, Barata P, Lima J, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. J Diab Compl. 2014;28(5):632-8.
19. Souza Leal L, Carvalho E, Tavares Pereira M, Xavier S, Càssia T, Rocha J, et al. Topical insulin therapy for healing of chronic skin ulcers. Diabetes Care. 2002;25(2):233–8.

Cite this article as: Baid S, Sharma RK, Sharma M, Sharma S. Efficacy of topical insulin versus normal saline in promoting granulation tissue formation and healing in diabetic foot ulcers: a prospective non-randomized interventional comparative study. Int Surg J 2025;12:1492-6.