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Effect of Local Insulin Injection for Wound Healing in Cases of Diabetic Foot Ulcers – A Randomized Control Trial

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KEYWORDS

Diabetic foot ulcers, Insulin therapy, Wound healing, Granulation tissue, Patient satisfaction, Hospital stay

ABSTRACT:

Background: Diabetic foot ulcers (DFUs) are a significant complication of diabetes, affecting millions worldwide and often leading to amputations. Local insulin therapy has shown promise in enhancing wound healing in DFUs by promoting a reduction in inflammation and collagen deposition.

Objective: To evaluate the effectiveness of local insulin injections in promoting granulation tissue formation and improving outcomes in patients with DFUs.

Methods: This was a comparative prospective randomized study conducted at the Department of General Surgery, Aarupadai Veedu Medical College and Hospital, Pondicherry. A total of 102 patients, aged 20-65 years with non-healing DFUs for more than three weeks, were included – randomised, one group receiving local insulin injections with normal saline dressings and the other group receiving only normal saline dressings.

Results: The mean age of patients in the insulin and saline groups was comparable ($p > 0.05$). A significant reduction in ulcer size was observed by day 14 in the insulin group compared to the saline group ($p < 0.05$). Granulation tissue formation was significantly accelerated in the insulin group from day 3 of dressing, with a higher incidence of healthy granulation tissue ($p < 0.05$). Patient satisfaction was significantly higher in the insulin group (100%) compared to the saline group (13.7%) ($p < 0.05$).

Conclusion: Local insulin therapy significantly improved ulcer healing outcomes compared to normal saline, with faster reduction in ulcer size, earlier appearance of healthy granulation tissue, and higher patient satisfaction.

Introduction

Diabetic foot ulcers impact a significant number of individuals worldwide, with an annual estimates ranging from 9.1 to 26.1 million cases. It is estimated that 15% to 25% of people with diabetes mellitus will experience a diabetic foot ulcer at some point during their lifetime.(1, 2) Among them diabetic foot ulcer is accounting for amputation in 85% of the individuals.(3, 4) Diabetic foot is a prevalent complication of diabetes. In patients with diabetic foot ulcers, various factors can contribute to the delayed formation of local wound granulation tissue, including elevated blood glucose levels (both locally and systemically), reduced efficiency of wound angiogenesis, and impaired fibrous tissue deposition.(5,

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6) Clinical and animal studies have suggested that local insulin treatment may enhance wound healing in diabetes.(7)

Insulin helps to reduce inflammation and increase collagen deposition, thereby accelerating the healing of burn wounds. Additionally, insulin injected diffusely into the wound aids in reepithelialisation. This effect is due to insulin's promotion of protein synthesis, which plays a crucial role in the wound healing process. The local application of insulin in treating nonhealing diabetic ulcers is now the focus of extensive research.(8, 9) Exploring the molecular pathways and cellular mechanisms through which insulin enhances wound healing could identify novel therapeutic targets and strategies for treating diabetic complications beyond foot ulcers.(10) This research also sheds light on the potential for accelerated wound healing through local insulin injections in diabetic foot ulcers, leading to quicker granulation tissue growth, shorter hospital stays, and improved patient adherence to treatment.(11, 12) The present study aimed to examine the impact of local insulin injections on granulation tissue formation in the wounds of patients with diabetic foot ulcers, while also assessing the curative effects and determining a safe dosage for local insulin application.

Materials and Methods

This comparative prospective randomized study was conducted among patients presenting to the Department of General Surgery at Aarupadai Veedu Medical College and Hospital, Pondicherry, who were conservatively treated for diabetic foot ulcers. The study included patients aged between 20 and 65 years with an ulcer duration exceeding three weeks. Patients with extensive or complete necrosis requiring immediate amputation at the time of admission, as well as those undergoing immunosuppressive therapy, radiotherapy, corticosteroids, or anticoagulants, and patients who discontinued therapy, were excluded from the study.

Routine investigations were conducted to assess blood sugar levels and evaluate the patients' diabetic status, allowing for appropriate management planning. The ulcer site was thoroughly cleansed using betadine and normal saline. A sterile tuberculin syringe was used to administer the calculated dose of insulin, diluted with normal saline, into the ulcer base. The insulin dose was determined based on the patient's fingertip blood glucose level. Half of the dose, calculated using a sliding scale, was diluted with normal saline to a total volume of 1 mL, and the other half was administered subcutaneously. Fingertip blood glucose levels were monitored at 30 minutes, 2 hours, and 4 hours post-injection to evaluate the effect of local insulin on systemic blood glucose levels. Granulation tissue formation was observed over a period of 7 to 10 days, and the data were statistically compared.

Statistical analysis was performed using SPSS v23.0, with data entered into an Excel sheet for processing. Results were summarized using mean, standard deviation, frequency, and percentage, and were presented in tables and charts. The unpaired t-test was employed for the comparison of continuous variables, while the chi-square test was used for categorical variables. A p-value of less than 0.05 was considered statistically significant.

Results

The present study included a total of 102 patients who met the inclusion criteria. The mean age of patients in the insulin group was 55.3 years, while in the normal saline group, it was 53.7 years. The mean age between the two groups was comparable ($p > 0.05$). Among the participants, there were 25 females and 26 males in the insulin group, and 19 females and 32 males in the normal saline group.

Assessment of ulcer size revealed a significant reduction by day 14 in the insulin group compared to the normal saline group ($p < 0.05$). Evaluation of granulation tissue showed significant healing in the insulin group from day 3 of dressing, with a higher incidence of healthy pink granulation tissue in the insulin group compared to the normal saline group ($p < 0.05$). Overall patient satisfaction was significantly higher in the insulin group (100%) compared to the normal saline group (13.7%) ($p < 0.05$).

Discussion

Insulin-like growth factor (IGF) is a crucial growth factor in wound healing, as in vivo studies show it stimulates cell proliferation, enhances angiogenesis, and promotes

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collagen synthesis – key processes for effective wound repair. Besides its systemic metabolic effects, insulin locally enhances wound healing by boosting cellular responses vital for tissue repair. The presence of insulin receptors on keratinocytes, fibroblasts, and endothelial cells highlights the importance of insulin signalling in skin wound repair.(13)

The present study included 102 patients meeting the inclusion criteria, with a mean age of 55.3 years in the insulin group and 53.7 years in the normal saline group, showing comparable age distributions ($p>0.05$). Gender distribution and rural residency were also similar between the groups. Consistent with these findings, Biradar et al.(14) reported a mean age of 51.2 years for patients, with similar age distributions and a male predominance. Additionally, the duration of diabetes, averaging 4.2 years, and mean HbA1c and fasting blood sugar levels were comparable between the groups.(14) In another study by Sanjay et al.,(15) 42 (70%) patients were in age range 41-60 years in all two groups. Majority 42 (70%) were males and 18 (30%) were females.

There was no incidence of hypoglycaemia in either of the groups. The blood glucose level was comparable between the groups in study by Sanjay et al.(15) in concordance to present study, Swaminathan et al., also recorded no significant difference in mean blood glucose level in both the group patients.(16) In the present study, ulcer size was significantly reduced by day 14 in the insulin group compared to the normal saline group ($p<0.05$). Significant healing and granulation tissue formation were observed in the insulin group from day 3 of dressing, with a higher incidence of healthy pink granulation tissue compared to the normal saline group ($p<0.05$). Primary closure was achieved in a higher percentage of patients in the insulin group (84.4%) compared to the control group (62.5%), while fewer patients in the insulin group required split-thickness skin graft (15.6%) compared to the control group (37.5%) in Bhamre et al. study.(17) In agreement with the present study, Biradar et al.(14) found a statistically significant reduction in wound surface area at days 7 and 15 between the insulin and saline dressing groups. The insulin group showed a 67.8±11.45% reduction compared to 49.51±18.21% in the saline group, with a statistically significant difference. Granulation tissue appeared in 6.08±2.15 days in the insulin group versus 9.48±4.21 days in the saline group, also showing a statistically significant difference ($p<0.001$).(14) Consistent with Thakur et al., the present study observed a significant reduction in wound surface area in the insulin group compared to the normal saline group. Additionally, the insulin group exhibited a significantly shorter average time for granulation tissue appearance (5.68 days) compared to the control group (11.24 days).(16) Insulin influences multiple aspects of cell behaviour, including proliferation, migration, and secretion. Keratinocytes are essential for re-epithelialization, while endothelial cells contribute to angiogenesis, and fibroblasts are crucial for extracellular matrix synthesis.(18, 19) Insulin's effects on these cell types synergistically promote efficient wound healing.(20)

Conclusion

In summary, the research underscores the efficacy of insulin therapy in wound dressing, showcasing notably enhanced ulcer healing outcomes compared to standard normal saline treatment. The insulin-treated group exhibited accelerated reduction in ulcer size, earlier development of healthy granulation tissue, and expedited negative conversion of pus cultures. Consequently, these advantages led to a reduced duration of hospitalization and increased patient contentment. These results strongly advocate for the superiority of insulin dressing over normal saline in fostering ulcer healing and minimizing hospital stays among individuals with chronic ulcers.

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Conflict of interest: Nil

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Table 1: Baseline characteristics between the groups

	Insulin		NS		p-value
	Mean	SD	Mean	SD	
Age (in years)	55.3	7.2	53.7	11.9	0.412
Duration of DM	7.2	2.8	7.7	3.1	0.44

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Ulcer duration (in days)	25.3	3.4	25.5	3.1	0.69
Weight (in kg)	69.5	9.3	69.9	9.2	0.5
Height (in cm)	161.1	4.4	158.3	5.7	0.12
PR per min	79.8	5.7	80.5	5.9	0.552
SBP (in mmHg)	120.1	8.4	118.4	9.4	0.75
DBP (in mmHg)	81.4	8.2	79.4	8.3	0.531
HB	11.5	1.3	11.4	1.1	0.12
TC	12106.3	1716.1	12317.8	1783.4	0.148
RBS/FBS	230.1	46.2	276.5	58.2	0.15
HbA1c	7.1	1.9	7.3	.6	0.06
Urea	30.9	4.0	29.5	5.1	0.117
Creatinine	.7	.1	.7	.1	0.887
Hospital stay (in days)	16.61	3.32	34.93	4.71	0.05*

Table 2: Comparison of change in glucose level between the groups

Glucose	Insulin		NS		p-value
	Mean	SD	Mean	SD	
Prior to Insulin	207.7	29.1	224.7	54.9	0.054
After 30min	159.5	19.3	166.7	39.2	0.242
After 2hr	115.3	13.7	117.3	24.6	0.606
After 4hr	158.2	20.6	164.4	27.0	0.193

Table 3: Comparison in change of ulcer size between the groups

Ulcer size (cm^2)	Insulin		NS		p-value
	Mean	SD	Mean	SD	
Day 0	19.2	15.9	19.8	12.5	0.132
Day 1	19.1	15.9	19.7	12.5	0.132
Day 3	18.5	15.9	19.7	12.5	0.132

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Day 7	17.5	14.5	18.8	12.2	0.097
Day 14	16.0	11.5	18.5	10.7	0.01*

Table 4: Comparison of change in granulation tissue between the groups

Granulation tissue		Insulin		NS		Chi square (p-value)
		Count	%	Count	%	
Day 0	Pale granulation	9	17.6	12	23.5	0.54 (0.46)
	Slough with pale granulation	42	82.4	39	76.5	
Day 1	Pale granulation	9	17.6	12	23.5	0.54 (0.46)
	Slough with pale granulation	42	82.4	39	76.5	
Day 3	Pale granulation	36	70.6	34	66.7	14.31 (0.01)*
	Pink granulation	9	17.6	0	0.0	
	Slough with Pale granulation	6	11.8	17	33.3	
Day 7	Pale granulation	27	52.9	39	76.5	27.51 (0.01)*
	Pink granulation	24	47.1	3	5.9	
	Slough with pale granulation	0	0.0	9	17.6	
Day 14	Healed	7	13.7	0	0.0	102.0 (0.01)*
	Pale Granulation	0	0.0	47	92.2	
	Pink healthy granulation	44	86.3	1	2.0	
	Slough with granulation tissue	0	0.0	3	5.9	