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Comparative evaluation of local insulin injection with normal saline dressing versus conventional normal saline dressing in diabetic foot ulcer

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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. This comparative prospective randomized study aimed to evaluate the effectiveness of local insulin injections in promoting granulation tissue formation and improving outcomes in patients with DFUs.
Materials & 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. Patients were divided into two groups: one group receiving local insulin injections with normal saline dressings and the other group receiving only normal saline dressings. Key exclusion criteria included patients requiring immediate amputation and those on immunosuppressive therapy. Data were collected on patient demographics, ulcer characteristics, an healing outcomes over 14 days. Statistical analysis was performed using SPSS v23.0.
Results: The mean age of patients in the insulin and saline groups was compared (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. These findings support the use of insulin dressing as a superior intervention for promoting ulcer healing and reducing hospital stays in patients with chronic diabetic foot ulcers.

Keywords: Diabetic foot ulcers, insulin therapy, wound healing, granulation tissue, patient satisfaction, hospital stay

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. Clinical and animal studies have suggested that local insulin treatment may enhance wound healing in diabetes [5].
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 re-epithelialization. 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 non-healing diabetic ulcers is now the focus of extensive research [6, 7]. 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. 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. 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 & Methods

This comparative prospective randomised study was conducted among the patients presenting to the department of General Surgery, Aarupadai Veedu Medical College and Hospital, Pondicherry who were treated for diabetic foot ulcers conservatively. The patients aged more than 20yrs and less than 65 yrs, with ulcer duration of more than 3 weeks were included. Patients with extensive and complete necrosis in the foot and who require immediate amputation at the time of admission to hospital and patients who were on immunosuppressive therapy, radiotherapy, corticosteroids, anticoagulants and who discontinued the therapy were excluded. All routine investigation were sent to check the blood sugar levels and access the diabetic status of the patient so that further management could be planned. The ulcer site was cleaned thoroughly with betadine and normal saline, sterile tuberculin syringe was used to inject the calculated dose of insulin diluted with normal saline in the base of the ulcer. Dose of insulin was calculated according to Fingertip blood glucose level, half of the calculated dose by sliding scale was taken and diluted with Normal Saline to make a total volume of 1ml and the other half was injected subcutaneously. Fingertip blood glucose levels were also monitored at 30 minutes, 2 hours and 4 hours to keep a check on the effect of local insulin on systemic blood glucose levels. Blood glucose levels were monitored at 30 minutes, 2 hours, and 4 hours post-injection. Granulation tissue formation was observed over 7-10 days, and data were statistically compared.

Statistical Analysis: Data were collected, entered into an Excel sheet, and analyzed using SPSS v23.0. Results were summarized using mean, standard deviation, frequency, and percentage, and represented with tables and charts. The unpaired t-test and chi-square test were used for comparing continuous and categorical data, respectively, with a p-value of less than 0.05 considered statistically significant.

Results

Present study included total of 102 patients fulfilling inclusion criteria. With mean age of patients 55.3 yrs in insulin group and 53.7 yr in normal saline group with mean age between groups were comparable. (p>0.05) among participants, 25 were female and 26 male in insulin group and in normal saline group 19 were female and 32 were male patients.

Table 1: Showing the baseline characteristics between the groups

	Insulin		NS		p-value
	Mean	SD	Mean	SD	
Age yrs	55.3	7.2	53.7	11.9	0.412
Duration of DM	7.2	2.8	7.7	3.1	0.44
Ulcer duration days	25.3	3.4	25.5	3.1	0.69
Weight	69.5	9.3	69.9	9.2	0.5
Height	161.1	4.4	158.3	5.7	0.12
PR per min	79.8	5.7	80.5	5.9	0.552
SBP mmHg	120.1	8.4	118.4	9.4	0.75
DBP 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 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 30 min	159.5	19.3	166.7	39.2	0.242
after 2 hr	115.3	13.7	117.3	24.6	0.606
after 4 hr	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	
D0	19.2	15.9	19.8	12.5	0.132
D1	19.1	15.9	19.7	12.5	0.132
D3	18.5	15.9	19.7	12.5	0.132
D7	17.5	14.5	18.8	12.2	0.097
D14	16.0	11.5	18.5	10.7	0.01*

On assessment of the ulcer size, there is significant reduction in the size of ulcer by day 14 in insulin group compared to the patients in normal saline group. (p<0.05).

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

Granulation tissue		Insulin		NS		Chi-square (p-value)
		Count	N %	Count	N %	
D0	Pale granulation	9	17.6%	12	23.5%	0.54 (0.46)
	slough with pale granulation	42	82.4%	39	76.5%	
D1	Pale granulation	9	17.6%	12	23.5%	0.54 (0.46)
	slough with pale granulation	42	82.4%	39	76.5%	
D3	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%	
D7	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%	
D14	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%	

On assessment of the granulation tissue, there is significant healing in insulin group from day 3 of dressing. Higher incidence of the pink healthy granulation tissue in insulin group compared to normal saline group. (p<0.05) Overall satisfaction was found to be significant with good response in insulin group (100%) compared to patient in 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 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 signaling in skin wound repair [8].

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 D *et al*. 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 [9]. In another study by Sanjay *et al*., 42 (70%) patients were in age range 41-60 years in all two groups. Majority 42 (70%) were males and 18 (30%) were females [10].

There was no incidence of hypoglycemia in either of the groups. The blood glucose level was comparable between the groups in study by Sanjay *et al*. [10] in concordance to present study, Swaminathan *et al*., also recorded no significant difference in mean blood glucose level in both the group patients [11].

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 [12]. In agreement with the present study, Biradar D *et al*. 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) [9]. 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) [11]. 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 extracellar matrix synthesis synthesis. Insulin's effects on these cell types synergistically promote efficient wound healing [13].

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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