

Original article:

Effectiveness of topical insulin in management of chronic diabetic foot ulcers

R. Swaminathan

Assistant Professor, Department of Surgery, TeerthankerMahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, INDIA.

Correspondence: R. Swaminathan

Abstract:

Introduction: Despite insulin treatment and a meticulously-controlled diet, approximately 15% of all patients with diabetes will, at some time, have non-healing wounds and this is the leading cause of lower extremity amputation. The purpose of this prospective, randomized study was to investigate the efficacy and safety of topical insulin in management of patients with chronic diabetic foot ulcers.

Materials and methods: 32 patients were enrolled by simple randomization to participate in study and divided in two groups, one with insulin dressings (Group A) and Group B with regular saline dressings. **Results:** The average depth of ulcer in insulin group was 8.7 mm before start of treatment whereas it was 8.2 mm in saline group. There was statistically significant difference ($p < 0.05$) in the improvement of ulcer depth wise in insulin therapy group before and after treatment. The average size of the ulcer was 4.1 cm^2 in insulin group and it was 3.9 cm^2 in saline group. Statistically significant difference ($p < 0.05$) in the improvement of ulcer size was found in study after treatment.

Conclusion: The use of topical insulin was found to be safe and effective in patients with diabetic foot ulcers. Results confirm that topically applied insulin can accelerate wound healing without any systemic side effects.

Key words: Insulin, Topical, Diabetes, Ulcer.

Introduction:

Despite insulin treatment and a meticulously-controlled diet, approximately 15% of all patients with diabetes will, at some time, have non-healing wounds and this is the leading cause of lower extremity amputation. Wound healing involve cell adhesion, migration, proliferation, differentiation, and apoptosis at cellular and molecular levels.^{1,2} Abnormalities of distinct factors of wound healing contribute to defective wound healing in diabetes ulcers, including decreased growth factor production, angiogenic response, macrophage function, collagen accumulation, epidermal barrier function, and

keratinocyte and fibroblast migration and proliferation.^{3,4}

Relative or absolute lack of insulin or its action is a hallmark of diabetes disease and defective insulin action in the skin contributes to wound healing defects in this disease.⁵ Due to underlying angiopathy and neuropathy, foot ulcers are quite common in diabetics.⁶ Conventional dressings were found ineffective in management of these ulcers as they respond poorly thereby increasing hospital stay and loss of quality working days of patients. Several therapeutic modalities are available to effect wound healing such as skin grafts, hydrocolloid dressings,

and high-protein diets, but some may not be economically suitable for the patient and/or may be associated with complications.⁷⁻⁹ Researches in past has shown that topical insulin accelerates wound healing in the skin of diabetic rats and humans.¹⁰⁻¹² Insulin stimulates the growth and development of different cell types and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts.^{13,14} The purpose of this prospective, randomized study was to investigate the efficacy and safety of topical insulin in management of patients with chronic diabetic foot ulcers.

Materials and methods:

Present study was conducted in department of general surgery, TeerthankerMahaveerMedical College and Research Centre, Moradabad, Uttar Pradesh(INDIA)during the period July 2013- Dec 2013. 32 patients were enrolled by simple randomization to participate in study and divided in two groups, one with insulin dressings (Group A) and Group B with regular saline dressings. Insulin mixtard (30/70) is selected for insulin dressings,

which is injected intralesionally into the wound during wound dressing.¹⁵

Patients with uncontrolled wound bleeding, severe malnutrition, severeinfection, immunodeficiency, age>75 years, renal failure, liver dysfunction, ischaemic limbs were excluded from study. Before the start of the treatment and once in a week thereafter, depth and size of the wounds were recorded. The recordings were carried for a period of 4 weeks or healing of ulcer whichever is earlier. Strict glycaemic control was brought in all the patients before study and also underlying anemia and hypoproteinaemia were corrected. Systemic antibiotics were given based on pus culture and sensitivity. Dressings were performed once in a day, with normal saline in one group and additionally insulin intralesional injection in another group. Verniercalipers was used to measure ulcer depth in its biggest diameter and ulcer area was used to define ulcer improvement. All patients participating in the study were informed and their consent taken.

Results:

Table 1: Demographics of study population

	Insulin Group	Insulin Group Percent	Saline Group Count	Saline Group Percent
Male	11	70%	9	61.5%
Female	7	30%	5	38.5%
Type 1 diabetes	1	10%	1	0%
Type 2 diabetes	17	90%	13	100%
Right foot	13	75%	11	61.5%
Left foot	5	25%	3	38.5%
Average size of ulcer	4.1 cm ²		3.9 cm ²	
Average depth of ulcer	8.7 mm		8.2 mm	

Table 2: Results of present study

	Depth of Ulcer (mm)		Size of Ulcer (cm ²)	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Group A*	8.7	2.8	4.1	1.6
Group B**	8.2	6.9	3.9	2.9

*Insulin Group, **Saline group

Demographics are presented in Table 1. Most common site of ulcer was right foot. Both in male and female patients it was type 2 diabetes which was more common. The average depth of ulcer in insulin group was 8.7 mm before start of treatment whereas it was 8.2 mm in saline group. There was statistically significant difference ($p < 0.05$) in the improvement of ulcer depth wise in insulin therapy group before and after treatment. The average size of the ulcer was 4.1 cm² in insulin group and it was 3.9 cm² in saline group. Statistically significant difference ($p < 0.05$) in the improvement of ulcer size was found in study after treatment. (Table 2)

Discussion:

Wound healing is a complex biological process that involves chemotaxis and neovascularization that comprises synthesis of extracellular matrix protein, components and remodeling of tissues. Chronic skin wounds like diabetic foot ulcers are more susceptible to bacterial contamination that further poses unfavorable complications; thus, many studies have reported on efforts and products to improve healing rates in management of these type of wounds which may, in turn, reduce complications.¹⁶⁻¹⁸

Present study showed statistically significant improvement in both area and depth of diabetic foot ulcers due to insulin therapy thus establishing the role of insulin in wound healing.

Experimental researches on animals in past shows that insulin signaling pathways are upregulated in the

wounded skin of normal rats, but in the wounded skin of diabetic subjects, these upregulations are treated with a topical insulin cream, an acceleration of wound healing occurs, in association with a recovery in the proteins of the insulin signaling pathways. Woost and colleagues have demonstrated an increase in the tensile strength of wounds in healthy rabbits with full-thickness, perforating, corneal incisions following 3 daily applications of insulin. Topical insulin does not alter serum glucose levels in these diabetic animals points to the correction of delays in reepithelialization in the diabetic cornea at the cellular rather than the systemic level.^{19,20}

Novel findings in the present study showing that topical insulin is efficacious for restoring normal reepithelialization in foot ulcers. Significant difference in present study groups can be explained as direct application of insulin to the injured cutaneous surface restores the decreased levels of DNA synthesis of basal epithelial cells to normal values, thereby stimulates active cell proliferation.

Conclusion:

The use of topical insulin was found to be safe and effective in patients with diabetic foot ulcers. Results confirm that topically applied insulin can accelerate wound healing without any systemic side effects.

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