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ORIGINAL SCIENTIFIC REPORT

Effectiveness of Topical Insulin Dressings in Management of Diabetic Foot Ulcers

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Abstract

Background Infected diabetic foot ulcers are always a problem for the surgeon, as well as, an economic burden upon the patient and state, in terms of increased hospital stay and cost of medications and dressings. Various methods have been devised for the treatment of infected wounds in history with varying results in different patients groups. The purpose of this study is to compare the effectiveness of topical insulin on the healing of diabetic foot ulcers with the conventional Pyodine® povidone iodine dressing. Our objective was to compare effectiveness of topical insulin with conventional Pyodine® povidone iodine dressings in frequency of healing of diabetic foot ulcers.

Materials and Methods It was a quasi-experimental study done at Pakistan Institute of Medical Sciences Islamabad over a period of 20 months from January 2015 to September 2016. One hundred ten patients were included in the study. Sampling technique used was non-probability consecutive. Patients were assigned into two groups, group A receiving treatment with solution of 30 International Units Insulin Regular in 30 ml of normal saline and group B receiving conventional dressing with normal saline. The wound were compared for both groups at the days 7, 14 and 21 for wound healing. Complete healing time of diabetic foot ulcers was determined from patients' followup visits in outpatient department. Data was by analyzed by SPSS 20.

Results A total of 110 patients were enrolled in the study. Patients were divided equally into both control and experimental groups. The mean age of the patients was 53.23 ± 6.21 years. The mean pre-treatment wound diameter was 4.81 ± 0.85 cm in the placebo group, while it was 4.84 ± 0.81 cm in the topical insulin group (CI 0.29–0.35, $P = 0.875$). The mean post-treatment wound diameter was 3.90 ± 0.76 cm in the placebo group, while it was 2.46 ± 0.57 cm in the topical insulin group (CI 0.44–0.58, $P = 0.022$). The mean wound difference was 0.91 ± 0.25 cm in the placebo group, while it was 2.4 ± 0.34 cm in the topical insulin group (CI 0.40–0.20, $P = 0.041$). The mean percent reduction in wound diameter was 19.2 ± 4.6% in the placebo group, while it was 49.7 ± 5.2% cm in the topical insulin group (CI 10.6–6.1, $P = 0.001$).

Conclusion There was significant contraction seen in the size of the ulcer in both the study groups depicting the healing process.

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Introduction

Diabetes mellitus is a state of persistent hyperglycemia resulting from the malfunction of the pancreas and defective insulin production or insulin resistance in peripheral tissues [1–3]. Diabetic foot ulcer is a complication of diabetes seen in approximately 15% of the population

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suffering from diabetes. Etiology of diabetic foot ulcers is multifactorial [4–6]. Ischemia, neuropathy, defective wound healing and wound infection result in chronicity of diabetic foot ulcer and lead to varying degrees of lower limb amputations [6, 7]. Another important factor responsible for delays in wound healing in diabetic patients has been postulated to be defective insulin action in the skin [7]. Management of diabetic foot ulcers continues to be an important challenge for surgeons. The existing management options to effect wound healing such as skin grafts, hydrocolloid dressings and negative pressure dressings have failed to produce adequate response, either because of high cost of treatment or associated complications [8]. The newer therapeutic modalities, which include use of growth factors and stem cells are expensive and their safety remains to be evaluated [9]. The role of insulin in the regulation of energy metabolism, protein synthesis, cell differentiation, and growth suggests that this hormone could also play an essential role in the regulation of wound healing [8, 9]. The insulin stimulates the growth and development of different cell types and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts [10]. An approach that is clinically less complicated and economically favorable for patients for healing chronic wounds seems necessary. The aim of the present study was to investigate the effect of insulin dressings on the growth of granulation tissue and wound healing in patients with a diabetic foot ulcer.

Materials and methods

This was a quasi-experimental study done at the diabetic foot clinic in The Surgical Outpatient Department of Pakistan Institute of Medical Sciences, Shaheed Zulfiqar Ali Bhutto University. The study was conducted from January 2015 to September 2016 after approval by the ethical committee. The sample size for the study was 110 patients. An equal number of patients (55 each) were allocated to each group (Intervention and Placebo). Sampling for the study was done by a non-randomized convenience sampling technique. Based on odd and even numbers, patients were divided into groups. Group A which was intervention group and group B was placebo group. Patients whose serial number was odd were placed in group A ($n = 55$). Patients with even serial numbers were included in group B. Patients were assigned to either group A or B. Diabetic foot ulcers of patients in group A were treated with normal saline 0.9% and insulin solution (30 ml 0.9% normal saline + 30 IU regular insulin) dressings. Diabetic foot ulcers of patients in group B were treated with normal saline 0.9% dressings. In the placebo group [group B ($n = 55$)], patients' wounds were dressed with normal saline solution only. For the purpose of blinding, syringes filled with normal saline and insulin mixture were prepared and labeled by the pharmacist. The investigators (surgeons) doing the dressings as well as the patients were unaware of the solution being used for dressing.

Inclusion criteria

The inclusion criteria:

1. Patients who were diagnosed with diabetic foot according to the 2010 Edition of the Clinical Practice Guidelines for the Prevention and Management of Diabetes Foot Complications (edited by the American Diabetes Association) presented to diabetic foot clinic on regular basis.
2. Participants who were able to and willing to participate in the study voluntarily who could come for dressings on a daily basis, or patients who agreed for admission for the duration of treatment were included in the study.
3. Patients with diabetes between the age group 35–85 years.
4. All the patients had diabetes, and the duration of diabetes was 5–20 years.
5. Patients having ulcer size ranging from 2 to 5 cm below the ankle on the dorsal or plantar aspect of the foot.
6. Patients with grade I and grade II ulcers of Wegener's Classification without significant growth of granulation tissue.
7. Patients with blood glucose levels between 110 and 130 gm/dl. Hemoglobin A1c was 7.1 ± 0.34.

The exclusion criteria

1. Patients with grade III, grade IV, and grade V ulcers of Wegener's classification.
2. Patients with severe peripheral limb ischemia with clinically impalpable posterior tibial artery.
3. Patients who were not on regular follow-up at the diabetic foot clinic or could not maintain regular follow-up and come daily for dressings.
4. Patients who developed systemic complications of diabetes and could not continue the treatment.
5. Patients who exhibited extensive and complete necrosis in the limb and required immediate amputation at the time of admission to the hospital.

Data collection procedure

This was a quasi-experimental study carried out at the Pakistan Institute of Medical Sciences, after approval from the ethical committee. A total of 110 cases of diabetic foot ulcers were included in the study. The study was done in the outpatient department (OPD) of PIMS. Patients presenting to diabetic foot clinics in surgical OPD with diabetic foot ulcers were included in the study. Each group comprised of 55 patients. These patients had been visiting the diabetic clinic regularly for diabetes control and management. Patients coming from outside Rawalpindi Islamabad who could not come regularly to diabetic foot clinic were offered admission in the hospital. Patients who agreed for admission were included in the study. Patients who refused admission were not included in the study. Based on their odd or even serial numbers as entered in the diabetic foot clinic register, patients were divided into two groups that are group A (n = 55) and group B. Patients in group A had daily dressings with normal saline and insulin solution (humulin regular insulin) 30 IU and in 30 ml normal saline mixture. In the placebo group [group B (n = 55)], patients' dressings were done only with normal saline. The fasting and random blood glucose levels were to be determined with one touch® blood glucose meter (Johnson & Johnson, Rochester, NY, USA). Written informed consent was obtained from all patients enrolled in the study prior to inclusion in the study. Dressing solutions were provided in 50-cc syringes. They were filled with normal saline + Insulin or normal saline by the pharmacist. The patient as well as surgeon and staff nurse who performed dressings were kept blinded to which solution was being used for dressing. Diabetic foot ulcer was assessed by the investigators at day 0, day 5, day 10, and day 14. Before the start of the treatment, ulcer mapping was done, and the size of the ulcer was documented. Depth of ulcers was also noted. The size was measured independently by two members of the investigating team. The mean of both these measurements was calculated and considered as the size of the wound. The second measurement of ulcer size was made 1 week after initiation of treatment. The recordings were carried for a period of 2 weeks and $\geq$ 50% reduction in the size of the ulcer was considered significant. Strict glycemic control was maintained in all the patients before the study, and underlying anemia and hypoproteinemia were evaluated and corrected. The dead necrotic tissue attached to the wound was surgically debrided. All the wounds were thoroughly washed with 0.9% normal saline before applying the dressing. Systemic antibiotics were given based on pus culture and sensitivity. During the course of dressing, the wound was observed for granulation tissue, wound discharge and control of infection. The outcome was measured in terms of reduction in wound size between the two groups. Data were tabulated, and the two groups were compared with reference to area and percentage reduction in the size of the ulcer. The study data was analyzed to evaluate the effect of topical insulin dressing over the saline dressing. SSPS 20 and Microsoft Excel were used in this analysis. Mean and standard deviation was calculated for descriptive variables, and an independent sample test was used for numerical data, and P value of <0.05 was considered significant.

Results

A total of 110 patients were enrolled in the study. Patients were distributed equally into both intervention group (group A) and placebo (group B). The mean age of the patients was 53.23 ± 6.21 years. The number of male patients in our study was higher (61) than the number of female patients (49). All the diabetic patients included in the study were kept on strict glycemic control by oral hypoglycemic. None of the patients required insulin for their glycemic control. In our study, the random blood sugar (RBS) values before dressing was 121.3 ± 40.1 mg/dl, whereas after dressing was 117 ± 39.7 mg/dl in group A, and in group B it was 119.3 ± 35.3 mg/dl, whereas after dressing was 120 ± 38.5 mg/dl which was comparable and statically not significant. No significant adverse effects of insulin absorption from ulcer such as hypoglycemia, sweating, palpitations headache were observed. In our study (as shown in Table 1), the mean pre-treatment ulcer size was 4.84 ± 0.81 cm in the group A while it was 4.81 ± 0.85 cm in group B (CI 0.29–0.35, P = 0.875). The mean post-treatment ulcer size at the end of study, i.e.,

Table 1 Ulcer size variation in placebo and treatment groups

Group	*N*	Mean	Median	SD
Pre-treatment wound size				
Placebo	55	4.81	4.9	0.85
Drug	55	4.84	4.8	0.81
Post-treatment wound size				
Placebo	55	3.9	4.03	0.76
Drug	55	2.4	2.5	0.57
Percent reduction in size of ulcer				
Placebo	55	19.2	18.4	4.6
Drug	55	49.7	48.3	5.2
Mean difference				
Placebo	55	0.91	0.85	0.25
Drug	55	2.4	2.3	0.34

2 weeks was 3.9 ± 0.76 cm in group B, while it was 2.4 ± 0.57 cm in the group A (CI 0.44–0.58, $P = 0.022$). The mean difference in ulcer size was 2.4 ± 0.34 cm in group A, while it was 0.91 ± 0.25 cm in group B (CI 0.40–0.20, $P = 0.041$). The mean percent reduction in wound diameter was 49.76 ± 5.2% cm in group A, while it was 19.2 ± 4.6% in group B topical insulin group (CI 10.6–6.1, $P = 0.001$). Statistical analysis of percent reduction in size of ulcer is shown in Table 2. This difference was statistically significant $P < 0.01$.

Discussion

Diabetes has become an epidemic in Pakistan. Pakistan ranks seventh among countries with highly prevalent diabetes [11, 12]. Diabetes and related complications have become a great socioeconomic burden on a developing country like Pakistan. There is a high prevalence of diabetes, glucose intolerance and diabetes-related complications in developing countries like Pakistan. Diabetic patients have a 15-fold higher risk of amputation, but half of these amputations can be prevented if these patients can be treated early, educated about foot care and have good glycemic control [11].

Diabetic foot ulcerations usually occur during the fifth to seventh decade of life [13]. In our study, the mean age of the patients was 53.23 ± 6.21 years. Our results are comparable to results from other studies from Pakistan that report 61% of patients was more than 55 years [11].

Insulin has long been recognized as an important contributor to wound healing, and many studies have demonstrated the positive effects of insulin on wound healing [14–16]. Insulin-like growth factor (IGF), which has a high sequence of similarity to the hormone insulin, has been shown through in vivo studies to stimulate the proliferation, migration, and extracellular matrix excretion by keratinocytes, endothelial cells, fibroblasts, and it even promotes the reformation of granulation tissue [15]. Human growth hormone receptors are present throughout the skin; insulin acts on these receptors and increases re-epithelialization as well as collagen content, granulation tissue, wound tensile strength, and local production of insulin-like growth factors by fibroblasts [16]. Insulin also stimulates proliferation and migration of human keratinocytes, which stimulates cell growth and enhances wound healing [16].

Topical formulations of insulin were utilized in the twentieth century in an attempt to control local hyperglycemia of peripheral tissue. However, later investigations have focused on topical insulin applications as it relates to IGF [13].

In this and other studies, an initial wound area correlated with wound healing rate—i.e., larger wounds healed at a faster pace than smaller wounds. However, in the current study, the healing rate in the treatment group was higher than in the control group, regardless of the initial wound size [13].

In a study by Genk et al., the number of days required for healing was 38 ± 17.03 days in group A1 and 44.3 ± 17.5 days in group B1. Both these groups A1 and B1 had diabetic patients. But the ulcers in group A1 required fewer number of days than group B1 [13]. In studies done by Pierre et al., in 1998, healing time was reduced from 6.5 ± 1.0 days with placebo to 4.7 ± 1.2 days during insulin infusion ($P < 0.05$), and study by Rezvani et al. [10] found a healing time of 41.85 ± 20.56 days in the insulin group and 43.50 ± 22.85 days in the normal saline dressing group. In other studies done by Greenway et al., Rezvani et al. [10],

Table 2 Statistical analysis of percent reduction in size of ulcer

	t test for equality of means		
	df	Sig. (2 tailed)	Mean diff
Percent reduction in size of ulcer			
Equal variances assumed	108	.000	− 8.63636
Equal variances not assumed	91.863	.000	− 8.63636
Mean difference			
Equal variances assumed	108	.000	− .30436
Equal variances not assumed	101.430	.000	− .30436
Post-treatment wound size			
Equal variances assumed	108	.022	.31527
Equal variances not assumed	107.976	.022	.31527

Comparison of percent reduction in size of ulcer between two groups was found to be statistically $P < 0.01$

Kanth et al. [17], wound healing rates were significantly accelerated in insulin groups and were comparable to our study.

Swaminathan in his study showed that topical insulin is efficacious for restoring normal re-epithelialization in foot ulcers. The significant difference in the study groups can be explained by the fact that the direct application of insulin to the injured cutaneous surface restores the decreased levels of DNA synthesis of basal epithelial cells to normal values, thereby stimulating active cell proliferation [18].

The average size of the ulcer was 4.1 cm^2 in insulin group, and it was 3.9 cm^2 in saline group in the study by Swaminathan R. Statistically significant difference ($P < 0.05$) in the improvement of ulcer size was found in study after treatment.(19) The mean wound difference was 0.65 ± 0.23 cm in the placebo group, while it was 0.95 ± 0.41 cm in the topical insulin group (CI 0.40–0.20, $P = 0.041$). The mean percent reduction in wound diameter was $17.32 \pm 4.04\%$ in the placebo group, while it was $25.96 \pm 6.3\%$ cm in the topical insulin group (CI 10.6–6.1, $P = 0.001$).

The results of the study by Stephan et al. [16] suggest significant improvement in the rate of pressure ulcer healing with topical insulin compared with normal saline. A randomized, double-blind, placebo-controlled study by Zhang XJ with insulin and zinc also reported wounds treated with insulin healed faster [19]. The dose of insulin (1 U/cm^2 wound area) used by Stephan et al. in their study also was found to be safe and effective for pressure ulcer management—none of the study participants in the insulin group developed hypoglycemia, and blood glucose levels before and after insulin application did not change significantly ($P > 0.05$).

Zhang and Lei studied the effectiveness of topical insulin in healing diabetic foot ulcers. They documented the growth of granulation tissue in the insulin group was more marked on day 7 after injection (24.87 ± 0.24). The necrotic tissue had been shed and partially exposed bone and tendon had become gradually covered by granulation tissue. These represented essential processes for wound bed preparation. The micro-vessel density (MVD) of the insulin group showed a rapid increase at day 7 (8.34 ± 0.48), which showed the consistency of the histology and gross observation results [20].

Neovascularization is critical for successful wound healing [18]. Efforts have been made to induce new blood vessel formation in order to enhance tissue repair [15, 19–21]. Mario Aurelio Martínez-Jiménez The difference in the number of blood vessels between 0 days and 14 days was 96 ($\pm$ 47) in the side treated with insulin ($P < 0.001$) and 32.88 ($\pm$ 45) in the side without insulin treatment ($P = 0.07$) [21].

Praveen et al. [22] showed the ulcer size on Day 1 was 48.33 ± 11.35 mm and 47.30 ± 11.30 mm in insulin group and saline group, respectively, and the complete healing time achieved in insulin versus saline group was 30.63 ± 6.5 days and 60.47 ± 23.31 days, respectively, with significant p value <0.0001.

There was significant contraction seen in the size of the ulcer in both the study groups depicting the healing process. However, the insulin group depicted better contraction rate. There was a statistical difference in the initial length and breadth of the wound size among both the groups. However, final length and breadth decreased significantly in both groups, retaining the insulin group with statistically significant reduction compared to normal saline group (mean $\pm$ SD; final length: normal saline vs. insulin 47.30 ± 11.3 vs. 48.33 ± 11.35; $P = 0.725$, final breadth: 36.47 ± 10.94 vs. 37.4 ± 7.5; $P = 0.701$) [22].

Conclusion

The results of our study have shown that topical insulin dressing is a safe and effective method used for diabetic foot ulcer healing when compared to normal saline. During the 2-week study, statistically significant differences in wound size were observed between saline and insulin gauze dressings. Because the study duration was short, and only superficial ulcers were included in study, the long-term effect of topical insulin on neuropathic ulcer healing and other chronic wounds remains to be examined.

Compliance with ethical standards

Conflict of interest No conflicts of interests or disclosures.

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