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Effectiveness of Topical Insulin for Management of Diabetic Wounds: a Comparison between Short and Long Acting Insulin

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Abstract

Non-healing diabetic wounds are one of the most common complicated wounds. Wounds of diabetic patients are often non-healing wounds that requires weeks of adequate and appropriate care for full recovery. The use of systemic insulin in some diabetic patients was reported to enhance the systemic inflammatory response. Thus, the present study was conducted to evaluate the effect of topical insulin application on diabetic wounds.Our objective was to compare the effectiveness of topical short acting and long acting insulin with combined with standard wound dressings in time and scores of healing of wounds in diabetic patients. Thirty adult patients of both sexes from the outpatient settings of the General and Plastic surgery wards at Minia University Hospital were included in the study. Patients were assigned into three groups, control group, patients applying short acting insulin and those applying long-acting insulin. The wounds were compared healing time, and scores for inflammation and pain at days 0, 14, and 21. The mean age of patients included in the study was 58.9±5.3years. The unit healing time for diabetic control group was 25.1±22.9 which was significantly higher that both topical insulin preparations receiving groups (10.02±5.4 and 5.1±2.4, respectively) with no significant difference between topical short and long-acting insulin applying groups. Upon scoring of wounds, the long-acting score of the short acting insulin was significantly lower than the control group at day 14 (p=0.001) while both topical insulin groups showed significantly reduced scores at day 21 compared to the control group (p=0.001 and p=0.009 for short and long-acting insulin, respectively). Both topical insulin treatments resulted in an acceleration of the wound healing process with no significant difference between short and long-acting preparations of insulin.

1. Introduction

One of the greatest characteristics of living organisms, including humans, is the ability of the body to heal wounds through cellular and molecular mechanisms. The process of healing involves many steps, cell adhesion, migration, reproduction, differentiation, and apoptosis. The wound healing process consists of successive and overlapping stages, thus a dysfunction at any stage can lead to impaired wound healing(1).
Diabetes is a major disease that causes pathological changes and poor wound healing. Twenty-five percent of diabetic patients will develop diabetic foot ulcers in their lifetime(2). It is widely accepted that hyperglycemia is not a single cause. Disturbance of glucose metabolism, irregularity of the inflammatory response, insufficient secretion of growth factors, and dysfunction in cell repair and cell signaling are all factors implicated in the wound healing complications of diabetes(3).Non-healing wounds especially of diabetics are one of the most common post-operative problems that a surgeon comes across. Non-healing wounds constitute a major problem that diabetic patients face. Approximately 15% of all patients with diabetes will suffer from non-healing wounds, even with insulin treatment and a well-controlled diet. Non-healing diabetic wounds are the major cause of lower extremity amputation (4, 5).
Since Banting's discovery of insulin in 1921, many benefits other than regulating blood glucose have been documented(6).The effect of insulin on wound healing has been reported in various animal wound models, including fracture wounds, skin ulcers and incision wounds(7). Clinically, insulin efficacy in wound healing was reported in burn patients receiving allographs (8). Previous studies found that insulin accelerates non-diabetic wound healing by improving angiogenesis and epithelial remodeling (9). Numerous studies reported the efficacy of insulin in wound healing but the effect of different forms of insulin (short and long-acting preparations) were not compared. Thus, we conducted a randomized clinical trial to evaluate the effect of the topical use of short and long-acting insulin in the rate of healing of diabetic wounds.

Methods

Patients

Thirty-type 2 diabetic patients of both sexes were randomly divided into three separate groups for comparing different treatments. The patients were recruited from the General surgery as well as Plastic and Reconstructive surgery departments at the Minia University Hospitals.

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The study was registered in the Pan Africa clinical trial registry (PACTR201909767694782) after obtaining an ethical approval from Minia University Hospital ethical committee.
Sampling for the study was done by a non-randomized technique, based on a number sequence 1 for control, 2 for topical short-acting insulin and 3 for topical long-acting insulin. Patients whose serial number was 1, 4, 7, 10...etc were placed in the control group (n = 10). Patients with serial numbersof2, 5, 8, 11...etc were included in short-acting insulin group. While patients assigned to serial numbers of 3, 6, 9, 12...etc were included in group 3 (long-acting insulin). The patients were unaware of the solution being used for their wound dressing and the examining physician for follow up was blind to the treatment too (Double-blind study). Nineteen patients used only oral anti-diabetic drugs while the others used subcutaneous insulin beside oral anti-diabetic drugs.

Inclusion criteria

Patients from 18-65 years, patients having pressure ulcers, post-operative surgical wounds, diabetic ulcer with a wound size less than 20cm² and classical signs and symptoms, and patients without any severe systemic disease, were included into the study.

Exclusion criteria:

Patientss less than 18 or more than 65, pregnant patients, patients with osteomyelitis, immunodeficient patients, patients with varicose ulcer, patients with liver disease, kidney disease, skin malignancy or who administer chemotherapy, and patients with wide wound size (more than 20cm^2), were excluded from our study.
All Patients agreed to be included in the study and written informed consents were obtained from all patients enrolled prior to inclusion in the study.

Treatment groups

The wounds of all patients were cleaned with sterile normal saline (0.9% NaCl), povidone iodine and treated with Mebo cream ® and fucidic acid cream (standard treatment).
In topical short and long-acting treated groups, wounds were cleaned with sterile normal saline and then irrigated with 4 units (0.1ml) of human soluble insulin (Actrapid® or Lantus®, respectively) in 1 ml saline for each 10 cm^2 of wound(7). The prepared solution was sprayed on the wound surface with an insulin syringe twice daily and the wound was left to dry, then treated with the standard treatment and then covered with sterile cotton gauze.
Diabetic wounds were assessed by the investigators at day 0, day 14, day 21. Wounds were measured with a sterile disposable ruler applied to the wound to define wound margins. The two largest perpendicular diameters were measured in centimeters(10). To calculate the wound area, these two diameters were multiplied to obtain the area of the wound in cm^2.Wounds photographs were taken by a digital camera (12-megapixel). Wound size was measured twice a week during the weekly visits of the patients to the hospital till complete healing of the wound.
The study endpoint was considered as wound epithelial tissue formation or complete wound healing. The wound healing rate was calculated as the difference between the initial wound size on the first day (day 0) and up to complete wound healing and recorded in terms of cm^2 / week as a marker of healing by Unit Healing Time (UHT)(11). UHT means the number of days required for healing per square cm of wound area. UHT was calculated with the following formula:

$$UHT = {}^{TDRH}/_{IAW}\, cm^2$$

Where, TDRH = total number of days required for healing and IAW = initial area of wounds in square centimeters

Assessment of blood glucose level

Although topical insulin was not expected to be absorbed systematically, random blood glucose levels were measured by a commercial glucometer (One touch select ®) 10 minutes before and 1 hour after application of topical insulin to assess safety.

Scoring system and healing parameters

PUSH scores (Pressure Ulcer Scale for Healing) is a wound assessment tool. PUSH scores were found to successful in assessing and monitoring acute wounds including skin lacerations, postoperative wounds, burns, and traumatic wounds. The PUSH tool is recommended for use in both research and in clinical practice as a measure of the outcome of wound healing interventions as well as an indicator of the quality of wound care services(12).
The PUSH model provides a simple, accurate and useful method for measuring wound healing through the evaluation of the following wound characteristics: surface area, exudates amount, and tissue type. The wound area scores were scored as (area in cm^2 = score): 0=0, <0.3 =1, 0.3-0.6 = 2, 0.7-0.1 =3, 1.1-2.0 =4, 2.1-3.0 =5, 3.1-4.0 = 6, 4.1-8.0=7, 8.1-12 =8 and 12.1-24=9. The exudate amount was scored as: none=0, light=1, moderate=2 and heavy=3. Finally, the tissue type scores were as follows: closed=0, epithelial tissue=1, granulation tissue=2, slough=4 and necrotic tissue=5. Each wound was given a sub-score for each of these wound characteristics. Then, these sub-scores were added together to get the overall score. The total scores measured over time provides an indication of improvement or deterioration in wound healing.

Statistical Analysis

Data were analyzed using SPSS version 21. Quantitative data were presented by mean and SD. Comparisons between groups were done using man-Whitney test, and Fisher exact. PUSH score comparison within same group was done by Friedman test.

Results

Demographics data

As shown in Table (1), the mean age of control group was 58.9±5.3, the mean age in the topical short-acting insulin was 55±8.2 while in the topical long-acting insulin it was 57±6.8. The percentages of males in the study were 50%, 70% and 40% in the control, the short-acting insulin and long-acting insulin, respectively.

Table (2) and Table (3) summarize the site and area of the wounds in our study with the different diabetic patients' group and the cause of these wounds.

Table 1: Demographic data of the studied subgroups.

	Control (N=10)	Short acting insulin (N=10)	Long-acting insulin (N=10)
Age			
Range	52-65	41-64	48-65
Mean ±SD	58.9±5.3	55±8.2	57.6±6.8
Gender			
Male	5(50%)	7(70%)	4(40%)
Female	5(50%)	3(30%)	6(60%)

Table 2: Site of the body affected among the studied groups

Area of the body affected	Control (N=10)	Short acting insulin (N=10)	Long-acting insulin (N=10)
Abdomen	10%	0	10%
Breast	10%	0	10%
Calcaneus's (Heel of foot)	10%	10%	30%
Carpus (Wrist)	10%	10%	0
Crus (Leg)	0	10%	10%
Hallux (Toe nail)	0	20%	10%
Hand (Manus)-Pollex or thumb	0	10%	0
Lower limp (small toe)	10%	10%	10%
Lower limp (sura region)	10%	10%	10%
Pes (Foot Pedal)	0	10%	0
Planta (Sor of foot)	0	0	0
Sacrum	10%	0	0
Tarsus (Ankle)	20%	10%	10%

Table 3: Cause of wounds among the studied groups

Cause of wound	Control (N=10)	Short-acting insulin (N=10)	Long-acting insulin (N=10)
Abscess	10%	10%	10%
Bed sore	0	0	20%
Diabetic Foot post-surgery abscess	10%	10%	0
Diabetic Foot Ulcer	40%	20%	50%
Inflamed cyst rupture	10%	0	0
Injury	10%	50%	10%
Pressure Ulcer	10%	10%	0
Surgery	10%	0	10%

Effect of topical insulin on blood glucose level

To ensure that the applied topical insulin does not affect the blood glucose level, we measured the blood glucose before application and 1 hour after application of insulin. Table (4) shows that no significant differences were observed.

Table 4: Blood glucose (BG) levels before and after topical application of insulin

Parameters	Control (N=10)	Short-acting insulin (N=10)	Long-acting insulin (N=10)
BG 10 mins before application	232.9±13.6	221.4±11.8	237± 14.8
BG 1hr after application	231.2± 13.6	221.0±11.236	232.4±17.5
P-value	0.149	0.512	0.08

Effect of topical insulin on wound healing

As shown in Table (5), the initial wound sizes among our study groups were 6.7±4.1,2.4±1.8 and 0.5-13.7 cm^2 for control, short-acting and long-acting insulin groups, respectively. The days required for healing were 27.1±9.9 for the control group, 18.2±8.2 for short-acting and 46.9±13.2 for long-acting insulin group. Figure (1) shows some representative photos from each group.

Table 5: Clinical characters of wound among the studied patients

	Control (N=10)	Short-acting insulin (N=10)	Long-acting insulin (N=10)
Size of wound			
Range	1.5-15	0.5-7	0.5-13.7
Mean ±SD	6.7±0.1	2.4±0.8	4.4±0.6
Day required for healing			
Range	28-63	12-42	7-35
Mean ±SD	46.9±0.2	27.1±0.9	18.2±0.2

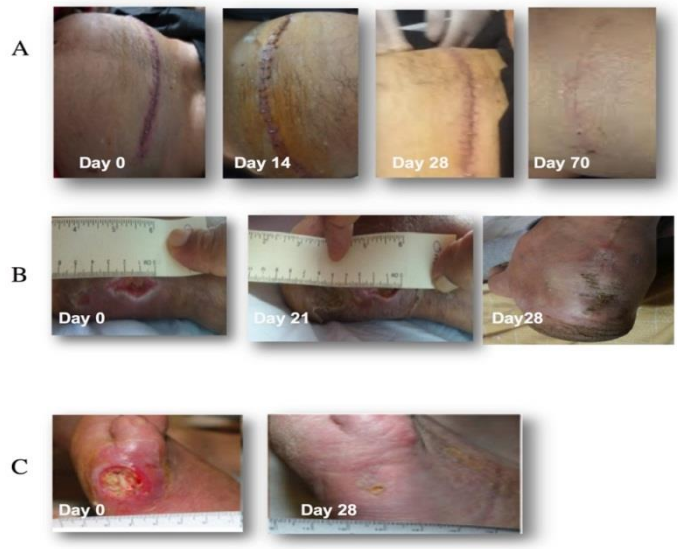

Figure 1: Effect of topical insulin on wound healing
Representative photographs showing wound healing from the three different groups.
A: A case of 63 years old diabetic male who had a surgical wound and received only standard treatment without insulin (control group).
B: A case of 50 years old diabetic male after application of topical short-acting insulin for 4 weeks.
C: A case of 60 years old diabetic female after application of topical long-acting insulin for 4 weeks.

Effect of topical insulin on UHT

To correct for the differences in the initial wound size in the different groups, the unit healing time (UHT) was used. A comparison between UHT in the three groups is shown in Figure 2.

As shown in this table, the mean values of UHT were: in the control group: 25.1±2.9, in short acting topical insulin: 10.02±0.4, and in long-acting topical insulin; 5.1±0.4.

When comparing the three groups, the UHT of both the short and long-acting insulin groups were statistically significant (p=0.02 and p=0.003) compared to the control group. No significant difference was found between the short and long-acting insulin groups

Effect of topical insulin on PUSH scores

The PUSH scores are shown in Table (6). At day 0, the mean score for the control group was 9.1±2.4, while in the short and long-acting insulin groups the scores were 8.1±2.1 and 11.9±1.6, respectively.

The mean PUSH score in day 14 was 6.7±0.6, 1.5±0.1 and 5.7±0.5 for the three groups respectively. At day 21, control group scored 5.8±0.9 while the short acting-insulin group scored 2.4±0.3 and the long-acting insulin group scored 2.4±0.3.

When comparing the three groups, the PUSH scores of short and long-acting insulin groups were statistically significant from control at day 14 and day 21when compared to the control group. No significant difference was found between the two treated groups at day 21.

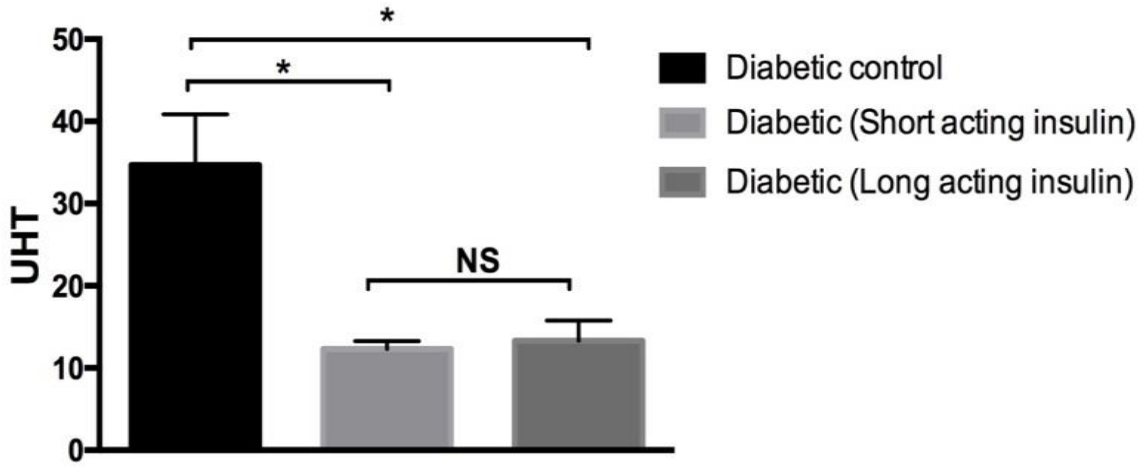

Figure 2: UHT in different treatment groups
Effect of treatment with topical insulin on unit healing time in different patients' groups.
*UHT: unit healing time; *: significance at p<0.05*

Table 6: The PUSH scores in different treatment groups

	Control (N=10)	Short-acting insulin (N=10)	Long-acting insulin (N=10)	p1	p2	p3
PUSH score in day 0				0.3	0.1	0.009*
Range	5-13	4-11	9-15			
Mean ±SD	9.1±0.4	8.1±0.1	11.9±1.6			
PUSH score in day 14				0.001*	0.003*	0.001*
Range	3-11	0-5	2-9			
Mean ±SD	6.7±0.6	1.5±0.1	5.7±0.5			
PUSH score in day 21				0.001*	0.009*	0.1
Range	1-10	0-4	0-9			
Mean ±SD	5.8±0.9	0.7±0.1	2.4±0.3			
P	0.0001*	0.0001*	0.0001*			

P: significance between the different time points within the same group, p1:significance between control & short-acting insulin, p2: significance between control &long-acting insulin, p3: significance between short-acting insulin vs long-acting insulin.

Discussion

Diabetes mellitus is described as a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The global incidence of diabetes is rapidly growing. It is estimated that more than 300 million people worldwide will have DM by 2025 (13, 14). Egypt ranked the 8th among countries for the number diabetic patients, the current estimate is 8.2 million which is predicted to go up to 16.7 million by 2045. Egypt will then climb to be rank number 6 in the list. It is the eleventh most important cause of mortality and is responsible for 2.4% of deaths. It is also the sixth most important cause of disability burden(15). The prevalence of diabetes continues to increase; therefore, the incidence of its complications (such as impaired wound healing) is also increased.

Wound healing is divided into three sequential and overlapping, phases: inflammation, proliferation, and remodeling. In the inflammatory phase, wound healing initiation starts with a series of biological events including release of vasoactive substances, cytokines and chemokines and activation of coagulation cascades. This is important for the regulation of the subsequent steps of proliferation and remodeling. Systemic insulin treatment was reported to ameliorate the systemic inflammatory response via inhibiting cytokine-induced neutrophil chemoattractant 1 (CINC-1), and CINC-2i as well as by reducing the expression of monocyte chemoattractant protein-1 (MCP-1). Insulin acts on human growth hormone receptors and enhancesthe reformation of the epithelium as well as collagen formation, granulation tissue, and the stimulation of fibroblasts to produce insulin-like growth factor (IGF) [16]. Insulin also stimulates migration and proliferation of human keratinocytes, which enhances cell growth and accelerates wound healing [16]. Early in the 20th century, topical formulations of insulin were used to control local hyperglycemia in peripheral tissue. However, later studies focused on the use of topical insulin as a stimulant of IGF release showing an ability to accelerate wound healing[13].

In our study, the mean age of the patients was 55 years. Our results are comparable to results from other studies that report 61% of patients was more than 55 years(16, 17).In our study, although initial wound areas varied between groups, the rate of wound healing in topical insulin groups was higher than the control group regardless of the initial size. This observation emphasizes the wound healing ability of insulin and is similar to previous findings (18). Many previous reports demonstrated the positive effects of insulin as a promotor of wound healing(19). The time required for complete wound healing shows great variations among different studies. Factors which may be responsible for these differences include: different initial wound size, site of the wound and the geographical region where the study was performed. For example, the number of days required for healing was reported to be 6.5 ± 1.0 days in placebo group and 4.7 ± 1.2 days during insulin infusion(20).While in the study by Rezvani et al. (18), the healing timeswere43.50 ± 22.85 days in saline dressing group and41.85 ± 20.56 days in topical insulin group. In another study done by Greenway et al.(21), wound healing rates were significantly accelerated in insulin groups and were comparable to our study.

The effect of topical insulin on wound healing was previously reported by Bhettani et al on diabetic foot ulcer. They explained the wound healing effect of insulin due to its ability to restore normal epithelium foot ulcers. This effect was explained in light of an ability of insulin to act on basal epithelial cells to restore the reduced levels of DNA synthesis to normal values, therefore activating cell proliferation (22). In the study of Zhang and Lei(23),they observed granulation tissue formation in topical insulin group which was evident after 7 days of application. They reported that the initial necrotic tissue covering the foot ulcer as well as the partially exposed bone and tendon was shed and gradually recovered by granulation tissue which is an essential step in wound healing. Insulin was reported in other studies to enhance the formation of new micro-vessels (neovascularization) which is also critical for complete wound healing (24).

Similar studies reported the same effect in different wound types. For example, a study by Stephan et al. (19)showed a significant improvement in the healing rate of pressure ulcer when using topical insulin compared to normal saline. A randomized placebo-controlled double-blindstudy using the combination of insulin and zinc also reported wounds a faster wound healing with insulin (25).

In our study, we used insulin in a dose of 0.4 U/cm^2 and found no systemic effect of this dose on blood glucose level. Other studies used higher doses such as (1 U/cm^2 wound area) used by Stephan et al. (25)where the authors also found the dose to be both safe and effective for pressure ulcer treatment.

Conclusion

Our study is the first to test the effect of topical insulin in Upper Egypt. The results of our study confirmed that topical insulin is both effective and safe for different wound types in diabetic patients. When comparing topical insulin groups to the standard wound dressing, statistically significant differences in wound healing rate and PUSH scores were recorded. However, the types of insulin used (short or long-acting) did not cause any significant different wound healing parameters. Thus, we recommend adding topical insulin application to the standard treatments of diabetic wounds especially those complicated and showing very delayed healing.

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