Evaluation of the Curative Effect of Topical Insulin Application on Burn Wounds of Non-Diabetic Patients with Minor to Moderate Partial Thickness Burns

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Background and aim
Burns are one of the most common traumatic conditions. Heat, chemicals, electrical currents, and radiation are all examples of physical or chemical factors responsible for burns. A previously conducted study of diabetic individuals found that the local injection of insulin for wound treatment promoted the processes of angiogenesis and fibrosis with no significant negative effects. This study was aimed at evaluating the curative effects of local insulin application in the treatment of minor to moderate partial-thickness burns in nondiabetic burned patients.
Patients and methods
This was a case–controlled, randomized clinical study of 50 patients of both sexes, nondiabetic, with minor to moderate partial-thickness burns, aged 20–55 years, who were allocated into two groups: the study group that received topical insulin application and the control group that received the usual treatment. Each group was treated for 14 days. The following items were assessed in both groups: wound healing time, pain, scar healing, incidence of adverse reactions, and Sequential Organ Failure Assessment score.
Results
Across the two groups, the wound healing time and the average number of burn dressing changes in the study group were substantially less than those in the control group. Before intervention, there was no significant difference in the level of pain, while after intervention, the study group was substantially less than the control group ($P<0.05$) in the level of pain and scar healing.
Conclusion
Topical insulin application was effective and harmless in the treatment of minor to moderate partial-thickness burns in nondiabetic burned patients.

Keywords:
burn, insulin, therapy

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Introduction

As stated by the data, around 11 million people are burned annually all over the world, with 180 000 dying as a result, ranking it as the fourth leading cause of trauma [1]. Insulin has been used in wound healing for several decades [2]. However, such advantages are only recorded in diabetes patients' and experimental animals' wounds. Therefore, that study was aimed at investigating the curative effects of local insulin application to treat minor to moderate partial-thickness burns in nondiabetic burned patients.

Patients and methods

This study had the approval of the local Institutional Review Board and the Research Ethics Committee, Faculty of Medicine, Suez Canal University, with the approval code 5467#. An informed consent form was signed by all patients. This study was carried out from January 2023 to October 2023. All patients were sent to the burn unit at Suez Canal University Hospital.

This was a case–controlled, randomized clinical study of 50 patients of both sexes, nondiabetic, with minor to moderate partial-thickness burn, aged 20–55 years, allocated into two groups: the study group that received topical insulin application and the control group that received the usual treatment. Each group was treated for 14 days.

Inclusion and exclusion criteria

Inclusion criteria: (a) nondiabetic patients who met this criteria fasting blood glucose less than or equal to 140 mg/dl before enrolment or 2-h postprandial blood glucose less than or equal to 200 mg/dl [3]; (b) patients with minor to moderate (≤15% total body surface area) partial-thickness burn with the following standards for diagnosis: a lot of blisters

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dispersed all over the burned area, bright red base, supple texture, and apparent discomfort; and (c) patients with no visible evidence of infection on the burned region or who were easily debrided and sterilized.

Exclusion criteria: (a) patients with serious cardiac disease and other medical disorders that were insufficiently controlled by medications; (b) patients who were discharged on their own responsibility from the burn unit before the burn was completely healed; (c) patients with inhalational injuries; (d) patients undergoing surgical intervention; (e) patients with signs of infection such as fever, an increased total leucocytic count, and a positive culture for bacteria; (f) patients who were at risk of infection due to contamination, the presence of a foreign body, or other factors; (g) patients with burns at any functional portions of the body, including joints, who may be functionally limited after healing due to scar contracture; (h) patients whose burn depth was still progressing (such as electrical burns or corrosive chemical burns); (i) patients whose burns were located in the face, perineum, etc., and were not easy to wrap; (j) women in the childbearing period; (k) patients with severe malnutrition; (l) patients who had an allergic reaction; and (m) patients who refused to take part in this study.

Therapeutic approach

After admission, the burned areas were simply debrided, wiped, or rinsed with normal saline, and an early, suitable fluid replacement was performed. For each 10 cm^2 of burned area, patients in the study group got topical application of 10 U (0.1 ml) of insulin crystal in solution with 0.9 ml of 0.9% saline, which is the safe cut-point dose without affecting blood glucose level [4]. An insulin syringe needle was used to spray the solution once daily on the burned area. While for every 10 cm^2 of burned area, patients in the control group got topical application of 1 ml of 0.9% saline.

In both groups, this topical treatment was administered once daily in the morning after meal, let dry for 30 min, and wrapped in sterilized cotton gauze. Patients were positioned in such a way that solution run-off from the burned area was avoided. Neither the patient nor the physician were informed about the treatment groups or measures for ensuring blindness. The participants agreed that they would receive treatment in stages until their burns healed.

The main goal was to ensure everyone's safety and minimize the side effects. General side effects were documented as headache, palpitation, and vertigo (due to hypoglycemia); meanwhile, in each group, glucose levels in the blood were determined through a glucometer 10 min before and 60 min after topical treatment application. All adverse effects were documented during the follow-up period.

Patient assessment

(1) Burn healing time: the time needed for burn healing and the number of dressing changes for each group were recorded. The burn healing period was clarified as the time between the patient's initial treatment and the burn being totally epithelialized with no exposed granulation tissue.
(2) Pain: the visual analog scale (VAS) [5] was applied to assess the severity of burn pain in each group before and after therapy. The assessment was carried out when the patient removed the burn dressing, disinfected it, and 5 min after the burn dressing change was finished. The final score was the mean of the three scores. The VAS score goes from 0 to 10, with 0 implying no pain and 10 implying severe and intolerable pain.
(3) Scar healing: the scar in the two groups was evaluated using the Vancouver scar scale [6] after wound healing. Scar thickness, elasticity, color, and vascularity are all measured on a scale of 0–15, with greater values implying more severe scars.
(4) Adverse reaction incidence: the frequency of adverse effects during treatment, such as hypoglycemia and allergic reactions, was recorded.
(5) The Sequential Organ Failure Assessment (SOFA) score [7] includes six organs: respiratory system support, coagulation profile affection, liver affection, circulatory disturbance, nerve affection, and kidney affection; each score is 0 to 4 points; the greater the score, the poorer the patient's prognosis.

Statistical analysis

Data were entered into the computer and analyzed using IBM SPSS software package, version 20.0 (Armonk, NY: IBM Corp). Categorical data were implied as numbers and percentages. A χ^2 test was used to investigate the association between the categorical variables. Alternatively, Fisher's exact test was used when more than 20% of the cells had an expected count less than five. For continuous data, they were investigated for normality by the Shapiro–Wilk test. Quantitative data were implied as range (minimum and maximum), mean, SD, and median. The Student t test was applied to compare two groups

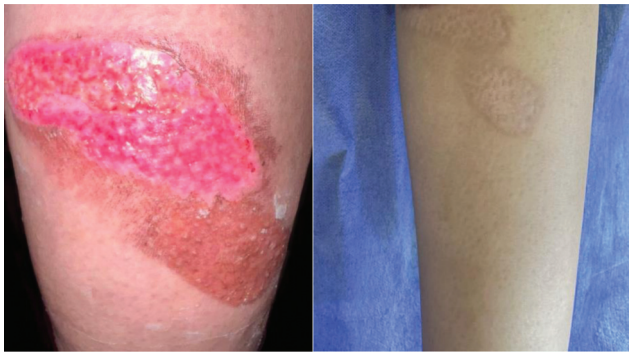
for normally distributed quantitative variables; on the other hand, the Mann–Whitney test was applied to compare two groups for not normally distributed quantitative variables. The significance of the obtained results was judged at the 5% level.

Results

In total, 50 patients with minor to moderate partial-thickness burns were allocated into two groups (25 patients in each). The study group included 12 (48%) males and 13 (52%) females with an average age of 36.4 ±8.64 years. The control group included 11 (44%) males and 14 (56%) females with an average age of 36.3±7.4 years. Extent of burn, depth of burn, cause of burn, site of burn, SOFA score, fasting blood glucose, and glycosylated hemoglobin did not differ across groups as the *P* value was more than 0.05 (Table 1).

The most common cause of burn injury in the study group was flame burn, which represented about 52% of cases, while in the control group it was hydrothermal, which represented about 60% of cases. According to the depths of burn, superficial partial thickness was

Figure 1



A partial-thickness flame burn on the outer side of the left leg of a 25-year-old female patient demonstrating the effect of topical insulin application (lesion at presentation on the left side and response 10 days after treatment on the right side).

Table 1 Comparison between the two studied groups according to different parameters

	Study group (*N*=25)	Control group (*N*=25)	Test of significance	*P* value
Age (years)				
Mean±SD	36.4±8.6	36.3±7.4	*t*=0.053	0.958
Median (minimum–maximum)	36 (20–50)	38 (23–50)		
Sex [*n* (%)]				
Male	12 (48)	11 (44)	χ^2=0.081	0.777
Female	13 (52)	14 (56)		
TBSA %				
Mean±SD	10.4±4.1	9.5±3.5	*t*=0.824	0.414
Median (minimum–maximum)	10 (3–20)	10 (4–17)		
Burn depth [*n* (%)]				
Superficial	17 (68)	19 (76)	χ^2=0.397	0.529
Deep	8 (32)	6 (24)		
Cause of burn [*n* (%)]				
Flame	13 (52)	10 (40)	χ^2=0.725	0.395
Scald	12 (48)	15 (60)		
Site of burn [*n* (%)]				
Upper limb	5 (20)	5 (20)		
Lower limb	9 (36)	10 (40)	χ^2=0.100	0.951
Trunk	11 (44)	10 (40)		
SOFA score				
Mean±SD	5±2.6	6.3±3.3		
Median (minimum–maximum)	5 (0–9)	7 (1–12)	*t*=1.636	0.108
HBA1C				
Mean±SD	5.6±0.8	6±0.7	*U*=212.500*	0.038*
Median (minimum–maximum)	5 (5–7)	6 (5–7)		
Fasting blood sugar (mg/dl)				
Mean±SD	77±7.4	80.2±8.6	*t*=1.414	0.164
Median (minimum–maximum)	75 (70–95)	80 (70–95)		
Healing time (days)				
Mean±SD	13.8±2.5	17.6±2.3	*t*=5.717*	<0.001*
Median (minimum–maximum)	14 (10–19)	18 (13–22)		

χ^2, χ^2 test; HBA1C, glycosylated hemoglobin; SOFA, Sequential Organ Failure Assessment; *t*, Student *t* test; TBSA, total body surface area; *U*, Mann–Whitney test. *P*: *P* value for comparing between the two studied groups. *Statistically significant at *P* value less than or equal to 0.05.

much more common than deep partial thickness in both groups (Table 1).

The previously mentioned indicators before and after intervention in each group were compared. The needed time for burn healing and the frequency of burn dressing changes in the study group were considerably low in comparison to those in the control group, as the *P* value was less than 0.05 (Tables 1 and 2) (Figs 1–3).

The mean VAS for wound pain before treatment was 5.1±0. 9 in the study group versus 5.6±0.9 in the control group, which decreased after treatment with a considerably lower score in the study group than those in the control group (0.9±0.7 vs. 1.8±0.7, respectively) ($P<0.05$) (Table 2).

Regarding the visual scar scale, there was statistical significance between both groups, as there was a considerably lower score in the study group than the control group (3.7±0.6 vs. 4.2±0.6, respectively) ($P<0.05$) (Table 2).

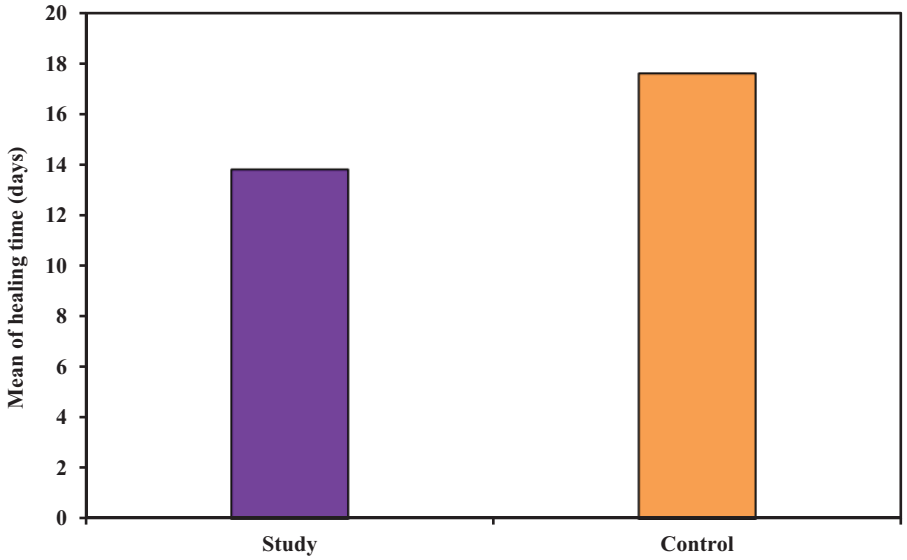
The overall frequency of complications was much lower in the study group than in the control group, with a total incidence of complications of about 12% in the study group and 44% in the control group, and the

Table 2 Comparison between the two studied groups according to different parameters

	Study group (*N*=25)	Control group (*N*=25)	Test of significance	*P* value
Number of dressing				
Mean±SD	6.9±1	9.4±2	*U*=65.500*	<0.001*
Median (minimum–maximum)	7 (5–9)	9 (7–15)		
VAS before treatment				
Mean±SD	5.1±0.9	5.6±0.9	*U*=217.500*	0.048*
Median (minimum–maximum)	5 (4–7)	5 (4–7)		
VAS after treatment				
Mean±SD	0.9±0.7	1.8±0.7	*U*=133.500*	<0.001*
Median (minimum–maximum)	1 (0–2)	2 (1–3)		
VSS after treatment				
Mean±SD	3.7±0.6	4.2±0.6	*U*=176.000*	0.002*
Median (minimum–maximum)	4 (3–5)	4 (3–6)		
Presence of wound infection [*n* (%)]	2 (8)	6 (24)	χ^2=2.381	^{FE}P=0.247
Dressing allergy [*n* (%)]	0	2 (8)	χ^2=2.083	^{FE}P=0.490
Bleeding [*n* (%)]	1 (4)	2 (8)	χ^2=0.355	^{FE}P=1.000
Folliculitis [*n* (%)]	0	3 (12)	χ^2=3.191	^{FE}P=0.235
Total incidence of complication [*n* (%)]	3 (12)	11 (44)	χ^2=6.349*	0.012*

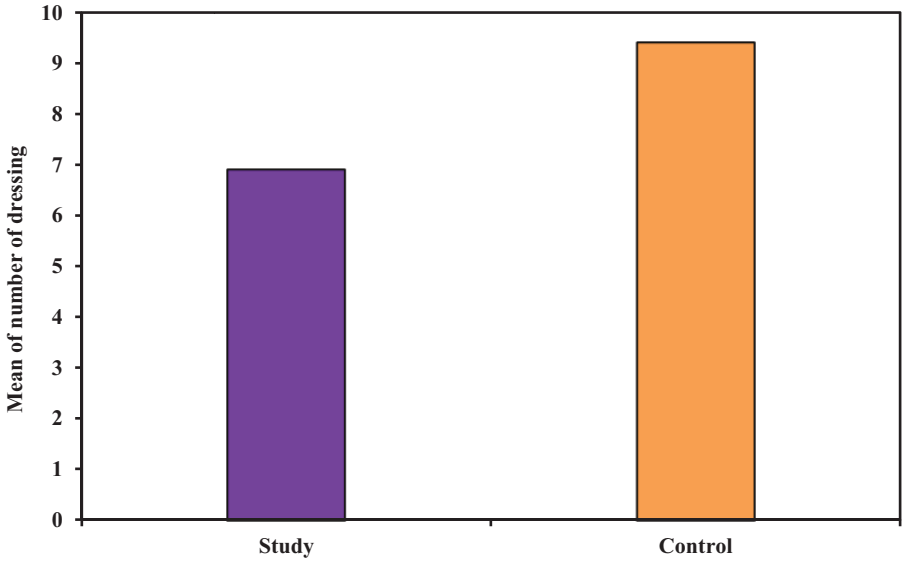
χ^2, χ^2 test; FE; Fisher exact; *U*, Mann–Whitney test; VAS, visual analog scale; VSS, Vancouver scar scale. *P*: *P* value for comparing between the two studied groups. *Statistically significant at *P*-value less than or equal to 0.05.

Figure 2



Comparison between the two studied groups according to healing time (days).

Figure 3



Comparison between the two studied groups according to number of dressing changes.

difference was considered significant as the *P* value was less than 0.05 (Fig. 4).

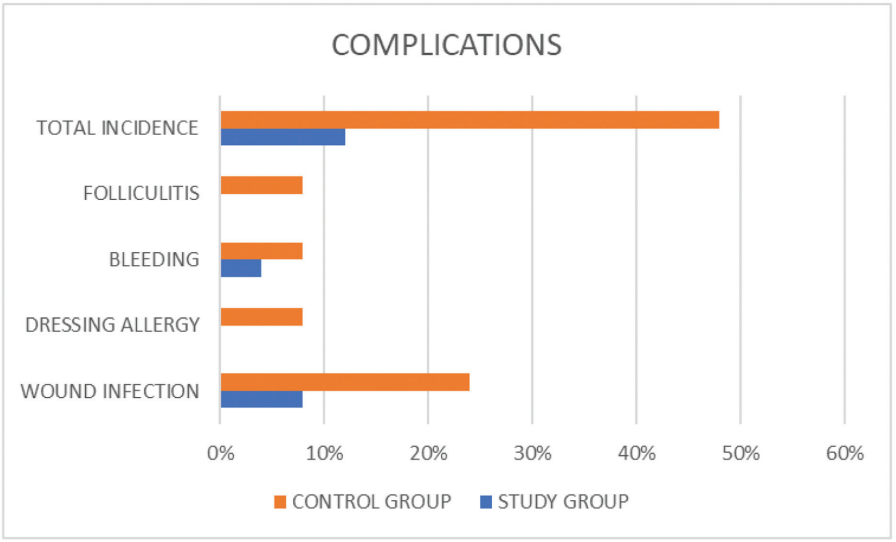
The most frequent complication in the study group was wound infection, while in the control group almost all complications were recorded, and the commonest was also wound infection at a rate of 24% (Table 2).

Discussion

Burns are heat-related damage to human tissues or organs as a result of flames, thermal fluids, steam, hot metals, and gases at high temperatures [8]. Considering the tissue injury induced by electrical currents, chemical compounds, radiation, and so on is the same as the pathological alterations and clinical processes generated by heat, it is also referred to as burns in clinical practice [9].

Insulin regulates the body's physiological metabolism, mostly through the mechanism of the tyrosine kinase receptor, by promoting the production of protein, glycogen, and fat in the body and controlling the metabolism of energy [10]. By local insulin application, the cells of skin tissue can regulate the

Figure 4



Comparison between the two studied groups according to complications events.

intracellular transport of glucose, the metabolism of protein, and the production of energy and synthesis of protein, thereby regulating cell growth, proliferation, and differentiation [11]. It is possible that insulin plays a beneficial role in the healing of wounds and burns in diabetic people. However, there is no evidence that local application of insulin is beneficial for burn injuries of varying depths in nondiabetic people.

In this study, patients were allocated into two groups, each containing 25 patients. Forty-eight percent of the patients in the study group were males, while 52% were females, with an average age of 36.4±8.64 years. The control group included 44% males and 56% females, with an average age of 36.3±7.4 years.

The extent of burn area, depth of burn, cause of burn, site of burn, SOFA score, fasting blood glucose, and glycosylated hemoglobin did not differ across groups as the *P* value was more than 0.05. The same finding was similarly recorded by Yang *et al.* [12].

The findings of this study revealed that the time needed for burn healing and the frequency of burn dressing changes in the study group were considerably lower than those in the control group, implying that topical application of insulin could considerably shorten the time needed for burn healing and decrease the frequency of dressing changes in patients with minor to moderate partial-thickness burns. Similarly, previous research [13] suggested that using topical insulin treatment for elderly patients with diabetic feet enhances wound healing and encourages patient recovery. Gang *et al.* [3] demonstrated that topical insulin application could considerably promote the healing of diabetic foot ulcers, reduce the needed time for wound healing, and reduce hospitalization.

Burn pain was considered the severest type of pain and was classified into six types, which include acute pain, background pain, postoperative pain, explosive pain, and others [14]. Acute burn pain is generated by the exposure of the skin nerve ending, the release of inflammatory mediators, local skin or tissue pressure, local tissue hypoxia, acidosis, ischemia, and tissue contraction on or around the lesion [14]. The severity or period of pain is determined by the patient's physical condition, burn degree, site, and source [14]. Burn discomfort is unavoidable throughout the process of wound healing or in the process of scar development and contraction during rest, but it can be eased by massage and distraction [14].

In this study, following treatment, the pain severity and healing of the scar in the study group were considerably lower than in the control group, implying that topical application of insulin had a positive influence on pain relief and healing of the scar tissue. Jibei *et al.* [15] demonstrated that recombinant human fibroblast growth factor in conjunction with topical insulin use has a positive role in the management of deep second-degree burns in diabetic patients, promoting healing of burn wounds, relieving pain, reducing the frequency of scarring, and causing few adverse effects.

After burn injury, the interplay of different cell repair factors, growth mediators, and extracellular matrix results in a complex and dynamic process of skin self-healing [16]. The phases of oxidative stress and the inflammatory reaction are the first to occur, followed by the phases of tissue repair and scarring, which comprise inflammatory reactions, granulation tissue creation, matrix synthesis, and remodeling [17]. Vascular endothelial growth factor (VEGF) is a platelet-derived growth factor that promotes the proliferation of the endothelial cell. It is secreted and activated in injury or other tissue trauma and is a major cytokine that supports the repair of different body tissues [17]. Topical use of nerve growth factor mixed with insulin was shown by Peilin *et al.* [18] to enhance wound healing, and its effect may be to regulate VEGF levels, stimulate angiogenesis, and improve local tissue hypoxia.

Zheng Hailong *et al.* [19] stated that topical insulin treatment might enhance the healing of diabetic wound patients, which would be advantageous to lower serum inflammatory markers, regulate VEGF levels, and minimize oxidative stress.

Finally, local insulin application enhances blood flow and the overall quality of cellular repair. As a result, these distinctions can be used to treat various types of minor to moderate burn wounds in diabetic and nondiabetic patients. The local insulin dose was chosen because it considerably stimulates healing, and a dose of 10 U of topical insulin is safe without influencing blood glucose levels, suggesting its potential utility in nondiabetic patients' wounds. The same was founded by Martínez-Jiménez *et al.* [4].

Conclusion

Topical insulin application in the treatment of minor to moderate partial-thickness burns in nondiabetic patients is a minimally invasive, cost-effective, and simple-to-implement treatment technique that

produces consistent results while not invalidating or precluding other approaches in the event of failure.

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Conflicts of interest

There are no conflicts of interest.

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