Original Article

Effect of Topical Insulin Versus Normal Saline Dressing in Healing of Diabetic Foot Ulcers

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Abstract

Background:

Diabetic foot ulcer is a common cause of admission in the surgical wards and sometimes the first presentation of this debilitating disease. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than normal saline dressing. This study aimed to compare the effect of topical insulin versus normal saline dressing in healing of diabetic foot ulcers at Rajshahi Medical College Hospital, Rajshahi. Aims and objectives: To assess the effect of topical insulin versus normal saline dressing in healing of diabetic foot ulcers. Methods: A total of 60 patients with diabetic foot ulcers were studied in different units of surgical ward of Rajshahi Medical College Hospital from July 2017 to June 2019. Patients were divided into two groups of 30 patients each that is group A (topical insulin) and group B (Normal saline). Ratio, mean, standard deviation, Pearson Chi-Square test were applied appropriately to this study. Results: Among the 60 patients, majority of the patients were males in both the groups (73.33% in group A and 80.00% in group B) with male to female ratio of 2.7:1 in group A and 4:1 in group B. The mean age in group A was 50.00±7.33 years and in group B it was 53.00±7.80 years, where P=1.00. Among patients with group A significant reduction of mean ulcer area was observed (314.30±171.26 mm2) with higher mean percentage reduction (15.30±3.28 percent), whereas, in group B the mean percentage reduction was significantly less (6.35±2.03 percent) with less reduction of mean final ulcer area (110.5±56.23mm2), where P<0.001. Conclusions: Topical insulin dressing provided better outcome in patients with diabetic foot ulcers by significant reduction in wound area when compared to normal saline dressing.

Keywords: Diabetic foot ulcers; Normal saline; Topical insulin; Wound healing.

Introduction: Diabetes mellitus is a clinical syndrome characterized by hyperglycemia caused by absolute or relative deficiency of insulin[1]. It is a very common ailment in our community[2]. Diabetes affects about 10% of our population and the prevalence of diabetes varies from 5.3% to 16.2%[3]. Most alarming is the steady increase in type 2 diabetes, especially among young and obese persons. An estimated 7% of Americans are affected with diabetes, and with the longevity of this population increasing, the prevalence of diabetes related complications will continue to rise[4].

Magnitude of diabetes mellitus in Bangladesh is increasing. Bangladesh will hold the 8th position according to the total cases of diabetes in adult population (20 to 79 years) in 2030[5].

The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. It is a chronic and potentially disabling disease which is reaching an epidemic proportion in many parts of the world. It is a major and growing threat to global public health[6].

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The vast majority of cases of the diabetes fall into two broad categories: those having little or no endogenous insulin secretory capacity (IDDM or type 1DM) and those who retain endogenous insulin secretory capacity but have a combination of resistance to insulin action and an inadequate compensatory insulin secretory response (NIDDM, or Type 2 DM)[6,7].

Long term complications of diabetes include retinopathy with potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations and Charcot joints and autonomic neuropathy causing gastro intestinal, genitourinary and cardiovascular symptoms and sexual dysfunction[8].

Diabetic foot disease is a common cause of admission in the surgical wards and sometimes the first presentation of this debilitating disease[4]. Patients with diabetes mellitus are at a higher risk of lower extremity complications as compared to their non diabetic counterparts. Every year 5% of the patients with diabetes will develop a foot ulcer. Approximately 15`% of all diabetics develop some foot problems during the course of their illness[8].

Foot ulcers carry a 25% risk of major amputation[8]. Therefore, the diabetic foot disease has major medical, social and economic consequences. It is very difficult to treat if proper protocol is not followed, resulting in longer hospital stay. Various studies show that it has the longest hospital stay as compared to other complications of diabetes.[9, 10]

One of the major causes of non-healing of ulcer in diabetes is infection. It is caused by a variety of micro-organism. Most common are Staphylococcus aureus and Pseudomonas aeroginosa which invade the wound and multiply, producing harmful toxic substances, causing destruction of tissue and disturbance in wound healing[11].

The management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear[11,12], daily saline or similar dressings to provide a moist wound environment[13], debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present[13,14], optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings[15, 16].

It is known that insulin stimulates the growth and development of different cell types, and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts[17-21]. Previous data, although not well controlled, showed that topical insulin accelerates wound healing in the skin of diabetic rats and humans[17, 22-28].

General objectives of this study to see the effect of topical insulin versus normal saline dressing in healing of diabetic foot ulcer and the specific objectives of this study to measure the reduction, complication and hospital stay of both groups treated by topical insulin and normal saline dressing.

Materials and method

This Randomized control study was carried out among the patients presented with diabetic foot ulcer in different surgery units of Rajshahi Medical College Hospital, Rajshahi from July 2017 to June 2019. Total patients 60, who fulfilled the following inclusion and exclusion criteria, were taken as study population. 30 patients were allocated to topical insulin dressing group and 30 to normal saline dressing group. The data obtained was tabulated, categorical data was expressed as rates, ratios and percentages and comparison was done using chi-square test. Continuous data was expressed as mean $\pm$ standard deviation and comparison was done using student unpaired t'test. A p 'value of less than or equal to 0.05 was considered as statistically significant.

Inclusion criteria:
- Diabetic patients between the ages 25 to 70 years.
- Patients having ulcers measuring more than one cm below ankle on the dorsum of foot.
- Patients with blood glucose levels between 110 and 130 mg/dL.
- Patients with grade I and II ulcers of Wegener's classification.

Exclusion criteria:
- Patients with grade III, IV and V ulcers of Wegener's classification.
- Patients with absent peripheral pulses, dorsal pedis artery, posterior tibial artery, anterior tibial artery.
- Patients who were not on regular follow-up.
- Patients not willing to enroll in the study.

Results

A total of 60 patients with diabetic foot ulcers were studied. Patients were randomized into two groups -

- Group A (n=30) – Patients in this group underwent dressing with topical insulin
- Group B (n=30) – Patients in this group underwent dressing with normal saline. Data was tabulated on Microsoft excel spreadsheet and analysis was done. The final results were tabulated as below-

Table I: Sex distribution

	Group A (Insulin) Sex (n=30)		Group B (Normal saline) (n=30)	
	Number	Percent	Number	Percent
Male	22	73.33	24	80
Female	8	26.67	6	20
Total	30	100.00	30	100.00
$X^2 = 2.53$		df = 1		p = 0.121

In this study majority of the patients were males in both the groups (73.33% in group A and 80% in group B) with male to female ratio of 2.7:1 in group A and 4:1 in group B.

Table II: Age distribution

Age group (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
<30	0	6.67	0	0.00
31 to 45	7	20.00	4	13.33
46 to 60	19	60.00	20	66.67
61 to 70	4	13.33	6	20.00
Total	30	100.00	30	100.00
$X^2 = 2.43$	df = 2			p = 0.321

In this study most of the patients were aged between 46 to 60 years in both the groups.

Table III: Mean age

Variable (years)	Group A (n=30)	Group B (n=30)
Mean	50.00	53.00
SD	7.33	7.80
P=0.100		

The mean age in group A was 50.00±7.33 years and in group B it was 53.00±7.80 years.
The mean age was comparable in both the groups (P=1.000).

Table IV: Distribution of patients according to duration of diabetes

Duration (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
<5	3	10	2	6.67
6 to 10	21	70	17	56.67
11 to 15	4	13.33	5	16.67
>15	2	6.67	6	20.00
Total	30	100.00	30	100.00
$X^2 = 4.12$		df=3		P=0.208

In this study most of the patients in both the groups (70% in group A and 56.67% in group B) had duration of diabetes between 6 to 10 years. The duration of diabetes comparable in both the groups (P=0.208)

Table V: Mean duration

Variable (years)	Group A (n=30)	Group B (n=30)
Mean	8.41	10.45
SD	3.26	5.21
		P=0.051

The mean duration of diabetes in group A was 8.41±3.26 years and in group B 10.45±5.21 years suggesting the mean duration of diabetes was comparable in both the groups (P=0.051).

Table VI: Ulcer details - Onset

Duration (Years)	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
Traumatic	10	33.33	18	60.00
Spontaneous	20	66.67	12	40.00
Total	30	100.00	30	100.00

In the present study, 66.67% patients had spontaneous onset of ulcer in group A compared to 40.00% in group B & 33.33% patients had traumatic onset in group A compared to 60% in group B. However the onset of ulcer was comparable in both the groups (P=0.121)

Table VII: Wound culture

Culture	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
Positive	20	66.67	20	66.67
Negative	10	33.33	10	33.33
Total	**30**	**100.00**	**30**	**100.00**

In the present study wound culture was positive in 66.67% & negative in 33.33% of patients each in both groups.

Table VIII: Isolates

Isolates	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
E. Coli	10	50.00	11	55.00
Klebsiella	3	15.00	2	10.00
Staphylococcus Aureus	3	15.00	4	20.00
P. Vulgaris	3	15.00	2	10.00
MRSA	1	05.00	1	05.00
Total	**20**	**100.00**	**20**	**100.00**

In this study the most common organism was E.Coli in both the groups (50% in group A and 55% in group B).

Table IX: Assessment of wound area

Assessment	Group A (n=30)		Group B (n=30)		p
	Mean	SD	Mean	SD	value
Initial area (mm^2)	2053.13	932.82	2253.63	889.94	0.525
Final area (mm^2)	1738.83	774.08	2143.13	835.73	0.121

In the present study the mean initial ulcer area in group A was 2053.13±932.82 mm² in group A which reduced to 1738.83±774.08 mm². Similarly in group B the mean initial ulcer area in group B was 2253±889.94 mm² which reduced to 2143.13±835.73 mm².

Table X: Reduction of wound area

Assessment	Group A (n=30)		Group B (n=30)		p
	Mean	SD	Mean	SD	value
Reduction in area (mm^2)	314.3	171.26	110.5	56.23	<0.001
Percentage reduction (%)	15.30	3.28	6.35	2.03	<0.001

In this study among patients with group A significant reduction of mean ulcer area was observed (314.30±171.26 mm2) with higher mean percentage reduction (15.30±3.28 percent), whereas, in group B the mean percentage reduction was significantly less (6.35±2.03 percent) with less reduction of mean final ulcer area (110.5±56.23mm2), where P<0.001.

Table XI: Wound culture on day 14

Culture	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
Positive	6	20.00	14	46.67
Negative	24	80.00	16	53.33
Total	**30**	**100**	**30**	**100**
X^2= 1.83	df= 1			p=0.176

In the present study, the wound culture on day 14 was negative in 80% patients in group A compared 53.33% in group B. However no statistically significant difference was observed between the two groups (P=0.176).

Table XII: Isolates on day 15

Isolates	Group A (n=30)		Group B (n=30)	
	Number	Percent	Number	Percent
E. Coli	2	33.33	6	42.89
Klebsiella	2	33.33	2	14.29
Staphylococcus Aureus	1	16.67	3	21.42
P. Vulgaris	0	0.00	2	14.29
MRSA	1	16.67	1	7.14
Total	**6**	**100.00**	**14**	**100.00**

In the present study, the most common isolate on day 14 was E.Coli in group B (42.89%) and in group A it was E.Coli and P.vulgaris (33.33%).

Discussion

Since Banting's discovery of Insulin in 1921, many benefits beyond blood glucose regulation have been documented. Insulin was also used in the 1960s to treat diabetic wounds in humans, and more recently, insulin spray has been successfully used to treat patients with diabetic ulcers. Furthermore, this hormone has been used to treat burns in humans, rats, and rabbits with good success. With the strong evidence that insulin stimulates healing, thereby decreasing the time of wound closure, the underlying mechanisms of insulin-induced improved healing are far from being understood.[32]

It is known that insulin stimulates the growth and development of different cell types, and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts.[19-23] Previous data, although not well controlled, showed that topical insulin accelerates wound healing in the skin of diabetic rats and humans.[19,24-31]

Diabetic foot ulcers are common and estimated to affect 15% of all diabetic individual during their lifetime. Patient suffering from diabetic ulcer often require hospitalization. One of the major causes of non-healing of ulcer in diabetes is infection. It is caused by a variety of micro-organism. Most common are Staphylococcus aureus and Pseudomonas aeroginosa which invade the wound and multiply, producing harmful toxicsubstances, causing destruction of tissue and disturbance in wound healing.[5]

The management of diabetic foot ulcers requires offloading the wound by using appropriate therapeutic footwear,[13,14] daily saline or similar dressings to provide a moist wound environment,[15] debridement when necessary, antibiotic therapy if osteomyelitis or cellulitis is present,[16,17] optimal control of blood glucose, and evaluation and correction of peripheral arterial insufficiency. Numerous topical medication and gels are promoted for ulcer care and healing. Relatively few have proved to be more efficacious than saline wet to dry dressings.[17,18] The present study was undertaken to compare the effect of topical insulin and normal saline dressing in healing of diabetic foot ulcers.

The present two years hospital based randomized controlled trial was conducted in the Department of General Surgery, Rajshahi Medical College Hospital from July 2017 to June 2019. A total of 60 patients with diabetic foot ulcers were studied. Patients were divided into two groups of 30 patients each that is group A (Patients in this group underwent dressing with topical insulin) and group B (Patients in this group underwent dressing with normal saline).

In this males (73.33% in group A and 80.00% in group B) outnumbered females in both the groups. The male to female ratio was 2.7:1 in group A and 4:1 in group B (p=0.121). Most of the patients (60.00%) were aged between 46 to 60 years in group A and 66.67% in group B. The mean age in group A was 50.00 ± 7.33 years and in group B it was 53.00 ± 7.80 years (p=1.000) suggesting the demographic characteristics of the study population were comparable in both the groups.

In this study most of the patients in both the groups (70.00% in group A and 56.67% in group B) had duration of diabetes between 6 to 10 years (p=0.208). The mean duration of diabetes in group A was 8.41 ± 3.26 years and in group B 10.45 ± 5.21 years (p=0.051). These findings suggest the characteristic of diabetic history was comparable in both the groups.

In the present study, 66.67% patients had spontaneous onset of ulcer in group A compared to 60.00% with traumatic onset in group B (p=0.121). The wound culture was positive in 66.67% of patients each in both the groups. The most common organism was E. Coli in both the groups (50% in group A and 55% in group B) suggesting the equal distribution of patients with regard to ulcer characteristics.

In the present study the mean initial ulcer area in group A was 2053 ± 932.82 mm2 in group A which reduced to 1738.83 ± 774.08 mm2. Similarly in group B the mean initial ulcer area in group B was 2253 ± 889.94 mm2 which reduced to 2143.13 ± 835.73 mm2. However the mean ulcer area at beginning in the both the group was comparable.

Among patients with group A significant reduction of mean ulcer area was observed in group A (314.30 ± 171.26 mm2) with higher mean percentage reduction (15.30 ± 3.28 percent) whereas in group B the mean percentage reduction was significantly less (6.35 ± 2.03 percent) with less reduction of mean final ulcer area (110.50 ± 56.23 mm2) The difference between the percentage reduction and reduction of final ulcer area was statistically significant (p<0.001) showing significantly favourable outcome in patients who underwent normal saline dressing.

In the present study, the wound culture on day 14 was negative in 80% patients in group A compared 53.33% in group B. However no statistically significant difference was observed between the two groups (p=0.176). The most common isolate on day 14 was E.Coli in group B (42.89%) and in group A it was E. Coli and P.vulgaris (33.33%).

There is scarcity of the literature showing the comparison of topical insulin and normal saline in diabetic foot ulcers.

Literature demonstrates that, despite evidence of a significant role for topical insulin in the promotion of wound healing in several animal models,[18,33-38] there has been little work done in humans.[29] More research is needed to investigate a potential role for topical insulin in the management of wound healing.

A study[39] reported that, the insulin signaling pathways are up regulated in the wounded skin of normal rats, but in the wounded skin of diabetic animals these up regulations are blunted. However, when the wounded skin of diabetic rats were 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.

A randomized, double-blind, placebo-controlled trial25 was conducted to determine the safety and efficacy of topical insulin on healing in 45 patients (29 men, mean age for both groups 40.62 years, range 12 to 71 years) with no infected acute and chronic extremity wounds. Patients were randomly assigned to twice-daily topical application (spray) of 1 cc saline 0.9% for each 10 cm2 of wound with or without 10 units (0.1 cc) of insulin crystal. No patients developed signs or symptoms of hypoglycemia and glucose levels pre- and post application did not differ significantly. Time to healing did not differ significantly between treatment groups. Healing rates were affected by baseline wound area, patient age, wound type (acute versus chronic), and treatment group. The mean rate of healing was 46.09 mm2/day in the treatment and 32.24 mm2/day in the control group (p=0.029), independent of baseline wound size. In this study, the topical application of insulin was safe and effective.

In other studies done by Greenway et al.,[39] Kanth et al.,[40] Rezvani et al[41] wound healing rates were significantly accelerated in insulin groups and were comparable to my study

Overall, in this study, topical insulin dressing provided favorable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing had positive role in reducing the infection if present.

Conclusion
Based on the results of the present study it may be concluded that, topical insulin dressing provides favorable outcome in patients with diabetic foot ulcer by significant reduction in wound area when compared to normal saline dressing.

Authors' contribution
Abbas Uddin was involved in the conception, design, drafting, data collection, data analysis and report writing. Ayesha Hasina was involved in conception, designing of the study, collection and supervision of data collection, preparation of manuscript and editing the research report. Sajal Kumar was involved in data collection, compilation and supervision.

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