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To Study The Efficacy of Topical Insulin Vs Conventional Dressing on Wound Healing In Diabetic Foot Ulcers

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Abstract
INTRODUCTION
Diabetes Mellitus is known to man to be one of the oldest diseases. Chronic complications lead to microangiopathy and macroangiopathy. One of the most common reasons for hospitalization in diabetic patients is diabetic foot ulcer. Around 30% of admissions are accounted for the same. It is well known that the basic cellular and molecular mechanisms that result in wound healing involve cell adhesion, migration, proliferation, differentiation, and apoptosis are impaired in diabetes mellitus. In diabetic people wound fails to re-epithelialize normally making them prone to infection. This study was taken up to evaluate the efficacy of topical insulin on wound healing in diabetic ulcers.
METHODOLOGY
In this study 70 patients with diabetic foot ulcers were selected and patients satisfying the inclusion criteria were allocated into insulin (test n =35) and saline (control n =35) groups. Initial wound debridement was carried out and wound was regularly assessed periodically for the presence of slough, necrotic tissue and granulation tissue. Initial and final size of the ulcer was recorded and percentage reduction in wound surface area was estimated.
Statistical analysis of the data collected was done with p-value of ≤0.05 as an indicator of statistical significance.
RESULTS
In this study, we found that the difference in the mean final size of the ulcer in the insulin and saline group is large. This difference is highly significant with a p-value of <0.01 as per student independent t-test. The difference in the percentage of wound reduction between insulin and saline group is very highly significant with a p- value of <0.001 as per chi square test. There was a statistically significant difference in relation to presence of slough and necrotic tissue between insulin and saline group with a p – value of < 0.01 as per student independent t-test. There was a statistically significant difference in relation to presence of granulation tissue between insulin and saline group with a p – value of < 0.01 as per student independent t-test.
CONCLUSION
Topical insulin in diabetic foot ulcers proves to be efficacious
- *In reducing the wound surface area.*
- *Reduction in the amount of slough and necrotic tissue from the wound surface.*
- *Promotes early granulation tissue formation.*

Keywords: *Diabetic foot, topical insulin, slough and necrotic tissue, granulation tissue, diabetic foot ulcer.*

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I. Introduction

Diabetes Mellitus is known to man to be one of the oldest diseases. There has been a continuous increase in the prevalence of diabetes worldwide at a frightening rate due to change in lifestyle, obesity and physical inactivity.

78 million people in South east asian region are affected by diabetes mellitus and is expected to attain 140 million by 2040. WHO reports that India had 69.2 million people living with diabetes (8.7%) as per the

2015 data, among these more than 36 million people remained undiagnosed.[1] The number of diabetics is expected to increase to 109 million cases out of a total estimated population of 1.5 billion in India by 2035.The prevalence of impaired glucose tolerance test (IGT) is around 8.7% in urban area and 7.9% in rural area, 35% of this population develop type 2 diabetes mellitus, so India is facing a genuine crisis. Type 1 is considerably rarer.

Diabetes Mellitus (DM) is a metabolic disorder marked by chronic hyperglycemia along with defective metabolism of carbohydrates, lipids and proteins. Individuals with controlled blood sugar levels are less likely to develop diabetic complications. Diabetic ketoacidosis (DKA), hypoglycemia, hyperosmolar hyperglycemic nonketotic syndrome (HHNS) are the acute complications. Chronic complications lead to microangiopathy and macroangiopathy causing diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, peripheral vascular disease, atherosclerosis and infections.

Diabetic foot ulcers are one of the major complications of diabetes and accounts for 30% of hospital admissions. Despite proper insulin treatment and a strict diabetic diet 15% of diabetic population develop non-healing ulcers which lead to amputations of the lower limb significantly.[2]

Management of diabetic foot ulcers includes control of existing infection by diligent antibiotic administration, local wound care, offloading the wound with use of proper therapeutic footwear, wound debridement (in case of presence of necrotic tissue), control of blood sugar levels and assessment of peripheral arterial state.

In the present day there are various types of dressings available and these form a pivotal part in the healing of foot ulcers. Wound healing is complex process involving cell adhesion, migration, proliferation, differentiation and apoptosis at both cellular and molecular levels.[3,4]

Topical dressings comprise as one of the modalities of care for diabetic foot ulcers. Different types of moist dressings and topical agents are used in the modern day for wound healing. Topical Insulin has proved to be efficacious in promoting wound healing by activating serine-threonine kinase (AKT) and extracellular signal regulated protein kinase (ERK) pathway.

II. Aims And Objectives

AIM:

To study the efficacy of topical insulin v/s conventional dressing on wound healing in diabetic foot ulcers in terms of

- Presence of granulation tissue
- Presence or absence of slough.
- Percentage reduction in wound surface area. Wound covered with granulation tissue.

Materials And Methods

PATIENT SELECTION

From February 2016 to July 2017, 70 Patients who were admitted with diabetic foot ulcers under Department of General Surgery, SRM Medical College, Hospital and Research Centre were selected for the study.

INCLUSION CRITERIA

1. Age group>20.
2. Patients of either sex.

EXCLUSION CRITERIA

1. Patients who have been operated for diabetic foot earlier.
2. University of Texas wound Classification System stage C and D, grade 3.
3. X-Rays showing features of osteomyelitis.
4. Doppler showing gross atherosclerotic changes and venous abnormalities like varicosities.
5. Uncontrolled diabetes.
6. Other clinically significant medical conditions that would impair wound healing including renal, hepatic, haematological, immunological, neurological diseases and malignancies.

PROCEDURE

- After getting Ethics committee clearance and obtaining patients consent, patients satisfying the inclusion criteria underwent initial wound debridement, by removal of necrotic debris, frank slough and foreign body. They were then subjected to necessary investigations such as Haemogram, FPG, RPG, HbA1C, Renal function test, Liver function test, Coagulation Profile, Doppler studies, X-rays and wound swab or pus culture & sensitivity. All the participants were allotted a number and then using a Random Number Generator they were allocated into two groups by the investigator after conducting the initial wound assessment.

- Initial assessment (sq.cm) was done by investigator and then allocated into Insulin group (Test) and Normal Saline group (control) in non-biased manner.

- Visual scoring of the wound was done based on the percentage of slough, necrotic tissue and granulation tissue present. Grading of the ulcer was done using the University of Texas wound Classification System.

- Ulcers of both groups were thoroughly debrided sequentially and antibiotics were administered according to culture sensitivity.
- The test group ulcers were cleaned with normal saline and then gentle irrigation of human soluble insulin was done over the ulcers (0.1ml of insulin in 1ml of normal saline for each 10 cm^2 of wound). Once the wound was dry the wound was covered with sterile dressing.
- The saline group ulcers were cleaned with normal saline and covered with sterile dressing.
- The study participants were not aware of the type of dressing/ treatment (insulin or saline) that was being received by them.
- The ulcers in both groups were inspected after removal of dressing and analyzed according to the visual scoring system on day 0,3, 5, 7, 13 and >20^{th} day for both the groups for
  - For the presence of granulation tissue in percentage.
  - Presence or absence of slough in percentage.
  - Percentage reduction in wound surface area.
  - Signs of wound infection: redness, collection or discharge.
  - Adverse effects of insulin if any.

III. Results

Majority of the patients 65.8% are less than 60 years in insulin group and in control it is 64.2%. There is no significant difference between Insulin group and saline group patients age distribution. It was assessed and confirmed using chi square test. Majority of the patients 74.3% are males in insulin group and in control it is 83%. No characteristic deficit was seen between Insulin and saline group patients gender distribution. Similarity of sex distribution was assessed using chi square test. Majority of the patients 74.3% are males in insulin group and in control it is 83%. No characteristic deficit was seen between Insulin and saline group patients gender distribution. Similarity of sex distribution was assessed using chi square test 80.0% of the patients have grade 2 ulcer in insulin group and 85.7% in saline group. Significant difference between both groups patient's ulcer grading is not seen. Similarity of ulcer grading was assessed using chi square test. 48.6% of patients in insulin group and 57.1% of patients in saline group have ulcers of size < 20 cm^2. Similarity of the initial size of ulcer is assessed using chi square test. Before treatment,13 cm^2 is the mean ulcer size in insulin group and 14.51 cm2 in control group, the difference of mean between the two groups is 1.51 cm^2, this difference is small and it is not statistically significant difference.

After treatment, 8.94cm^2 is the mean ulcer size for insulin group and is 11.60 cm2 is the mean ulcer size in control group, the difference of mean is 2.66cm^2, this difference is large and the difference is statistically significant. domain 1- physical health shows significance value of 0.03 with mean 2 and S.D. 2.4. In control group Statistical significance was calculated using student independent t-test. 77.1% patients in insulin group achieved 26 - 50% percent of wound reduction whereas 22.9% patients achieved the same in saline group. On Day 0, the mean percentage of slough and necrotic is 62.91% for insulin group and it is 63.80 % for saline group, with a mean difference of 0.89 %, and the difference is not statistically significant. On Day >20, the mean percentage of slough and necrotic is 0.69% for insulin group and it is 5.03 for saline group, difference of mean is 4.34%, this difference is large and it is statistically significant difference. On Day 0, the mean percentage of granulation tissue is 5.46% for insulin group and it is 4.20 for saline group, difference of mean is 1.26 %, this difference is small and it is not statistically significant difference. On Day >20, the mean percentage of granulation tissue is 92.74% insulin group and it is 78.86 for saline group, difference of mean is 13.88% this difference is large and it is statistically significant difference.

Table 1 : Age distribution between insulin and Saline group

Age		Group				Chi square test
		Insulin		Saline		
		n	%	n	%	
	≤ 50 years	5	14.3%	13	37.1%	
	51 -60 years	18	51.5%	13	37.1%	$\chi 2=5.36$ =0.15(NS)
	61 -70 years	6	17.1%	6	17.1%	

	>70 years	6	17.1%	3	8.7%	
	Total	**35**	**100.0%**	**35**	**100.0%**	

Table 2: Gender distribution between insulin and saline group

Gender	**Group**				**Chi square test**
	Insulin		**Saline**		
	n	**%**	**n**	**%**	
Male	**26**	**74.3%**	**29**	**82.9%**	
Female	9	25.7%	6	17.1%	**χ2=0.76** *p*=0.38(NS)
Total	**35**	**100.0%**	**35**	**100.0%**	

Table 3: Ulcer Grading between insulin and saline group

Grade	**Group**				**Chi square test**
	Insulin		**Saline**		
	n	**%**	**n**	**%**	
G1	7	20.0%	5	14.3%	
G2	28	80.0%	30	85.7%	χ2=0.40*p*=0.52(NS)
Total	**35**	**100.0%**	**35**	**100.0%**	

Table 4: Distribution of initial size of ulcer between insulin and saline group

Size of Ulcer	**Group**				**Chi square test**
	Insulin(n=35)		**Saline(n=35)**		
	n	**%**	**n**	**%**	
5-10 cm2	16	45.7%	10	28.6%	
10 -20 cm2	17	48.6%	20	57.1%	χ2=2.91 P=0.23(NS)
>20 cm2	2	5.7%	5	14.3%	

Table 5: Distribution of final size of ulcer between insulin and saline group

Size of Ulcer	**group**				**Chi square test**
	Insulin(n=35)		**Saline(n=35)**		
	n	**%**	**n**	**%**	
5-10 cm2	19	54.3%	10	28.6%	
10 -20 cm2	16	45.7%	23	65.7%	χ2=6.05 P=0.05 *(S)
>20 cm2	0	0.0%	2	5.7%	

Table 6: Comparison of the average size of ulcer before and after between insulin and saline group

Size of ulcer		**Group**				**Chi square test**
		Insulin		**Saline**		
		Mean	**SD**	**Mean**	**SD**	
	Before treatment	13.00	5.03	14.51	5.15	t=1.24 *p*=0.21(NS)
	After treatment	8.94	3.61	11.60	4.74	t=2.63 *p*=0.01**(S)

Table 7: Distribution of percentage reduction of wound compared between insulin and saline group.

Percentage of reduction	**Group**				**Chi square test**
	Insulin		**Saline**		
	n	**%**	**n**	**%**	
<10 %	1	2.9%	1	2.9%	
11 -25%	7	20.0%	26	74.2%	χ2=21.25 P=0.001***(S)
26 -50%	27	77.1%	8	22.9%	
Total	**35**	**100.0%**	**35**	**100.0%**	

Table 8: Day wise comparison of visual scoring of slough and necrotic tissue between insulin and saline group

Follow up DAY	**Group**				**Mean difference**	**Student independent t-test**
	Insulin		**Saline**			
	Mean	**SD**	**Mean**	**SD**		
0	62.91	24.19	63.80	21.98	0.89	t=0.16 *p*=0.87 (NS)

3	52.49	24.66	52.77	23.23	0.28	t=0.05 *p*=0.96 (NS)
5	29.60	28.72	31.26	21.98	1.66	t=0.27 *p*=0.78 (NS)
7	8.94	12.66	18.00	13.72	9.06	t=2.87 *p*=0.01** (S)
13	4.00	6.00	10.51	10.82	6.51	t=3.11 *p*=0.01** (S)
>20	0.69	1.35	5.03	6.45	4.34	t=3.90 *p*=0.01** (S)

Table 9: Daywise comparison of visual scoring of granulation tissue between insulin and saline group

Followup DAY	**group**				**Mean Difference**	**Student independent t-test**
	Insulin		**Saline**			
	Mean	**SD**	**Mean**	**SD**		
0	5.46	9.37	4.20	9.70	1.26	t=0.55 *p*=0.58 (NS)
3	18.80	17.95	12.77	13.89	6.03	t=1.57 *p*=0.12 (NS)
5	40.51	22.10	28.11	18.68	12.4	t=2.53 *p*=0.01** (S)
7	63.86	20.88	48.66	22.75	15.2	t=2.91 *p*=0.01** (S)
13	81.26	13.86	61.86	25.01	19.4	t=4.01 *p*=0.01** (S)
>20	92.74	13.37	78.86	22.06	13.88	t=3.18 *p*=0.01** (S)



ULCERS WITH TOPICAL INSULIN ADMINISTRATION

Fig 1a: Day 0 **Fig 1b: Day14** **Fig 1c: Day 21**



Fig 2a: Day 0 **Fig 2b: Day 21** **Fig 2c: Week 5**


Fig 2d: Week 6 **Fig 2e: Week 8**

ULCERS WITH NORMAL SALINE DRESSING

IV. Conclusion

In our study to evaluate the efficacy of topical insulin on wound healing we conclude that topical insulin is an effective therapy in treating diabetic ulcer secondary to systemic therapy in the terms of reduction in size of the wound, early reduction in the amount of slough and necrotic tissue therefore reducing infective foci from the wound surface. Insulin stimulates keratinocyte migration and increases the rate of growth of fibroblasts which promotes early formation of granulation tissue and hence creating a healthy bed for any surgical intervention for secondary wound closure. Our study is comparable to a randomised double blinded controlled trial, S.E. Greenway[5] and et al concluded topical insulin accelerated wound healing in humans. A study[6] of a long standing non-healing scar of a 80 year woman after laparotomy, where NPWT showed failure of results, on the other hand topical insulin showed marked success with no systemic side effects like hypoglycaemia.

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