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Original Article

Surgery Section

Topical Insulin and Normal Saline in Chronic Diabetic Foot Ulcers- A Prospective Analytical Study

DAYANAND BIRADAR[1], MALLIKARJUN B PATIL[2], RAMAKANTH BALOORKAR[3], VIKRAM SINDAGIKAR[4], K MANOOP[5]

ABSTRACT

Introduction: Diabetic foot ulcers are important diabetes-related microvascular complications aggravated due to multiple pre-existing factors such as peripheral arterial disease, immune system factors, bone abnormalities, diabetic neuropathy, infections and repetitive external or minor trauma. Diabetic foot ulcers could lead to lower limb amputation if not managed appropriately.

Aim: To evaluate the use of topical insulin in chronic diabetic foot ulcers at a tertiary care centre.

Materials and Methods: This prospective analytical study of 12 months duration was conducted in Department of Surgery, in diabetic patients between the age group of 25 to 70 years, presenting for the first time with diabetic foot ulcer. A total of 60 patients were divided into two groups alternately as group A patients underwent dressing with topical insulin and group B patients underwent dressing with regular normal saline. Sterile transparent gauze was placed on the wound to mark the wound borders and the wound area measured. With the help of ruler the two largest perpendicular diameters were measured and these were multiplied to obtain the wound area in cm^2. Ulcers were cleaned with normal saline and a sterile gauze soaked with Human mixtard insulin and normal saline. Four units of 0.1 mL-Human mixtard insulin with 1 mL normal saline used for each 10 cm^2 of wound in group A. Data was analysed by using SPSS software. Chi-square test was used and p-value of <0.05 was considered as significant.

Results: Mean age distribution was 51.2±9.6 years and 50.6±10.9 years in group A and B, respectively. Mean HbA1c at admission was 6.3±0.9 and 6.1±0.8 in group A and B, respectively. On day 0,7,15 wound measurements were done. A statistically significant difference was noted in reduction of average surface area of wound at day 7, 15 between group A and B. Insulin dressing group showed better changes than saline dressing group. Percentage reduction of surface area of wound at day 15 was 67.8±11.45 in insulin dressing group and 49.51±18.21 in saline dressing group, statistically significant difference was noted. Average time required for granulation tissue to appear was 6.08±2.15 days and 9.48±4.21 days in group A and B, respectively, statistically significant difference was noted (p<0.001).

Conclusion: The application of topical insulin is secure and successful in patients with diabetic foot ulcers. Topically applied insulin can increase speed of wound healing and there are no chances of systemic side effects.

Keywords: Chronic wounds, Diabetes mellitus, Wound care

INTRODUCTION

Diabetes is the most common metabolic disease in modern world. This disease is attributed to change in lifestyle, obesity and physical inactivity. Diabetes Mellitus leads to micro-angiopathy and macro-angiopathy causing nephropathy, neuropathy, retinopathy, peripheral vascular disease, atherosclerosis and infections [1]. It is estimated that approximately 20% of hospital admissions among diabetic patients are due to diabetic foot ulcers and related complications [2]. Diabetic foot ulcers are mainly due to micro vascular lesions related to diabetes mellitus, aggravated by several predisposing factors, such as peripheral arterial disease, immune system factors, bone abnormalities, diabetic neuropathy, infections, repetitive external or minor trauma. Diabetic foot ulceration has deep rooted impact on patients suffering from social stigma, isolation, unemployment and financial burden due to extended treatment. Conventional dressings were found ineffective in management of diabetic foot ulcers as they respond poorly to treatment and increases hospital stay of the patient [3].

Diabetic ulcer wounds are enriched in proteases and support the premise that impaired growth factor availability may act as a rate limiting factor in healing of diabetic ulcer. Role of insulin in wound healing is documented in scientific studies. Insulin helps in tissue proliferation and healing by stimulating growth and development of keratinocytes, endothelial cells and fibroblasts [4]. Because of its low cost, incorporation of insulin in wound dressings can prove to be a better option to accelerate healing, still topical insulin is not used routinely [5]. There are many different type of moist dressings and topical agents used for wound healing. These dressings play a pivotal role in healing of diabetic ulcers. Topical insulin has proved to be efficacious in promoting wound healing by activating extracellular signal regulated protein kinase (ERK) pathway and serin threonine kinase (AKT) pathway. Insulin receptor, a trans-membrane molecule is activated by insulin, Insulin Growth Factor (IGF)-1 and IGF-2. It is one among tyrosine kinase receptor family which is found in all cell types, including keratinocytes and fibroblasts [6]. According to Liu Y et al., topical application of insulin in excision wounds stimulated keratinocyte migration [7]. P13K-AKT pathway involved in this keratinocyte migration activated a small GTPase as a molecule activated downstream P13K-AKT [8].

Present study was conducted to evaluate use of topical insulin in chronic diabetic foot ulcers at a tertiary care centre.

MATERIALS AND METHODS

This prospective analytical study was conducted in Department of General Surgery, Shri BM Patil Medical College Hospital and Research Centre, Vijayapura, Karnataka, India. Study period was of 12 months, from January 2019 to December 2019. Institutional Ethical Committee Clearance (ethical clearance number BLDE(DU)/IEC/309/2018-19) was taken for the study. Procedure was explained and a written informed consent was taken from patients, prior to participation. Sample size was calculated with anticipated mean difference of mean at end point between the

study groups as 2.1 and standard deviation as 2.0. A total of 76 patients were taken for study, 10 patients lost for follow-up and another six patients did not gave consent. Hence, a total of 60 patients were allocated into two groups, 30 each in topical insulin and normal saline based on the comparative method, alternately, patients were divided into two groups.

Group A- Patients underwent dressing with topical insulin,

Group B- Patients underwent dressing with normal saline.

All diabetic patients between the age group of 25 to 70 years, presenting for the first time with ulcers measuring more than one cm below ankle in dorsum of foot and blood glucose levels between 110 and 130 gm/dL were included in the study. Patients who have been operated for diabetic foot infections earlier (in the same foot), uncontrolled diabetes with HbA1c levels >8, patients with absent peripheral pulses in dorsalis pedis artery, posterior tibial artery, anterior tibial artery and who were not on regular follow-up were excluded from the study.

On admission detail history, clinical examination was done. Laboratory investigations such as Complete Blood Count (CBC), Fasting Blood Sugar (FBS), Post Prandial Blood Sugar (PPBS), Liver Function Test (LFT), Renal Function Test (RFT) blood group RH typing, Renovascular Disease (RVD), Hepatitis B surface Antigen (HBsAg). All other tests that were done were all comparable in both groups they did not affect much on the treatment strategy so they have not been highlighted, only the tests which are directly related to study have been mentioned. Anaesthetic fitness was taken. Surgical debridement of the patients were done and a sterile transparent gauze was placed on the wound and wound borders were marked. With the help of ruler the two largest perpendicular diameters were measured and wound area was calculated by multiplying these two diameters and area of ulcer was determined. Patients were alternately divided into two groups. Ulcers were cleaned with normal saline and a sterile gauze soaked with Human mixtard insulin and normal saline (4 units 0.1 mL-Human mixtard insulin in 1 mL normal saline for each 10 cm^2 of wound) was applied once daily, in group A. In group B, ulcers were cleaned with normal saline and covered with sterile gauzes. All patients were treated empirically with Inj. Amoxycillin-clavulanic acid and Inj. Metronidazole. Later antibiotics were changed according to pus culture and sensitivity reports. Daily dressing was done. Ulcer area was measured on day 1, day 7 and day 15. Reduction in the area of ulcer area was calculated at day 7 and day 15 in comparison with day 1 area of ulcer.

STATISTICAL ANALYSIS

Data was tabulated and the two groups were compared with reference to area and percentage of reduction. Study data was analysed using SPSS software and Microsoft excel software. Association of two qualitative variables was done by Chi-square test. A p-value of <0.05 was considered as statistically significant.

RESULTS

Total 60 patients were included for study and alternatively divided in two groups. Group A patients underwent dressing with topical insulin while group B patients underwent dressing with normal saline. Mean age distribution was 51.2±9.6 years and 50.6±10.9 years in group A and B, respectively. Mean HbA1c at admission was 6.3±0.9 and 6.1±0.8 in group A and B, respectively. Difference between group A and group B was statistically not significant [Table/Fig-1]. On day 0, 7, 15 wound measurements were done. A statistically significant difference was noted in reduction of average surface area of wound at day 7, 15 between group A and B. Insulin dressing group shown better changes than saline dressing group. Percentage reduction in average surface area of wound at day 15 was 67.8±11.45 in insulin dressing group and 49.51±18.21 in saline dressing group, statistically significant difference was noted. Average time required for granulation tissue to appear was 6.08±2.15 days and 9.48±4.21 days in group A and B respectively, statistically significant difference was noted (p<0.001) [Table/Fig-2].

Characteristic	Group A	Group B	p-value
Age (in years)	51.2±9.6	50.6±10.9	>0.05
Male: Female ratio	19:11	17:13	>0.05
Duration of diabetes (in years)	4.2±2.6	3.8±2.9	>0.05
Mean HbA1c at admission	6.3±0.9	6.1±0.8	>0.05
Mean fasting sugar level at admission	134.4±25.6	130±28.9	>0.05

[Table/Fig-1]: Clinical characteristics of study patients.
values are in mean±SD, chi-square test was used and* p-value of <0.05 is considered significant

Parameters	Group A	Group B	p-value
Average surface area of wound (cm^2) at day 0	4.21±1.99	3.98±2.02	>0.05
Average surface area of wound (cm^2) at day 7	2.06±1.43	2.98±1.78	<0.05*
Average surface area of wound (cm^2) at day 15	1.44±0.93	2.31±1.21	<0.05*
Percentage reduction (%)	67.8±11.45	49.51±18.21	<0.05*
Average time required for granulation tissue to appear (in days)	6.08±2.15	9.48±4.21	<0.001**

[Table/Fig-2]: Comparison of reduction of ulcer size.
values are in mean±SD, chi-square test was used and *p-value of <0.05 is considered significant and **p-value <0.001 is highly significant

DISCUSSION

Based on the 2015 prevalence data from the International Diabetes Federation, it is estimated that foot ulcers develop in 9.1 million to 26.1 million people with diabetes annually worldwide [9]. A systematic review and meta-analysis of the global prevalence of diabetic foot ulcers showed that the global prevalence of diabetic foot ulcers was 6.3%, higher in males than in females, and higher in type 2 than in type 1 diabetic patients [10]. Diabetic foot ulcers respond poorly to conventional dressings and thus these patients are over-burdened with prolonged hospital stay and increased financial overload. A normal working man loses his quality working days and this becomes a major economic crisis to the concerned family. There is defective wound healing in diabetes due to decreased manufacture of growth factors, poor angiogenic response, macrophage function, collagen accumulation, epidermal barrier function and keratinocyte and fibroblast proliferation and migration [11-14]. Insulin acts as a growth factor, in several preclinical studies insulin proved to stimulate angiogenesis, collagen formation, matrix formation and granulation tissue proliferation. Insulin stimulates the growth and development of different cell types and affects proliferation, migration and secretion by keratinocytes, endothelial cells and fibroblasts [15]. Topical application of insulin in diabetic patients with ulcers has a significant improvement in healing of the ulcer.

In present study majority of the patients were male (36, 60%) than female (24, 40%). Jyothylekshmy V et al., had 200 (72.2%) males and 77 (27.7%) females in their study [16]. The age range in present study was between 25 and 70 and the mean age was found to be 51.2±9.6 years and 50.6±10.9 years in group A and B, respectively. Mean reduction in average surface area of wound at day 15 was 67.8±11.45 in insulin dressing group and 49.51±18.21 in saline dressing group, statistically significant difference was noted. Average time required for granulation tissue to appear was 6.08±2.15 days and 9.48±4.21 days in group A and B, respectively, statistically significant difference was noted (p<0.001). Similar findings were noted by Pandey S et al., Prasad A et al., and Mahidhar RV et al., [17-19]. Significantly increased proliferation of granulation tissue was noticed in most of the patients who received local insulin therapy and improvement of the wound in the form of diameter and depth in insulin group.

Limitation(s)

The present study was of a small sample size, limited duration of follow-up and patients with controlled diabetes. Further research is needed with large sample size and longer follow-up, in patients with fasting sugar values more than 180 mg/dL. Also other insulin preparations can be tried with ethical permission.

CONCLUSION(S)

The use of topical insulin is safe and effective in patients with diabetic foot ulcers. Topical insulin in diabetic foot ulcers has a significant improvement in ulcer healing as evident by significant reduction in ulcer area. Further large scale studies are needed to document role of insulin in the healing of diabetic foot ulcers.

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PARTICULARS OF CONTRIBUTORS:

1. Assistant Professor, Department of General Surgery, BLDE Hospital (DU), Vijayapura, Karnataka, India.
2. Professor and Head, Department of General Surgery, BLDE Hospital (DU), Vijayapura, Karnataka, India.
3. Associate Professor, Department of General Surgery, BLDE Hospital (DU), Vijayapura, Karnataka, India.
4. Associate Professor, Department of General Surgery, BLDE Hospital (DU), Vijayapura, Karnataka, India.
5. Postgraduate, Department of General Surgery, BLDE Hospital (DU), Vijayapura, Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Mallikarjun B Patil,
OPD No. 4, Genral Surgery, BLDE Hospital (DU), Vijayapura-586101, Karnataka, India.
E-mail: drdayanandbiradar@gmail.com

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