



A COMPARATIVE STUDY BETWEEN EFFICACY OF TOPICAL INSULIN AND NORMAL SALINE DRESSINGS IN DIABETIC FOOT ULCERS.

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ABSTRACT

Introduction: One of the most prevalent problems a surgeon encounters is chronic wounds, especially those that do not heal. The development of agents for wound healing is the subject of ongoing study. Insulin is one such substance that stimulates connective tissue. **Objective:** To evaluate the effectiveness of topical insulin dressings with traditional saline dressings in the healing of chronic diabetic foot ulcers (DFUs), in terms of the size of the ulcer, the amount of time spent in the hospital, and any side effects. **Materials and Methods:** In this prospective longitudinal study, the patient's willingness to receive topical insulin therapy was used to separate the study population (n=100) into study group (insulin group, n=50) and Control group (saline group, n=50). Using paired and unpaired Student's t-tests, the variables of ulcer surface area, granulation tissue formation and length of hospital stay were compared. A p-value of < 0.05 was deemed significant. **Results:** In the study group, the mean ulcer surface area was 40.4 cm², compared to 37.6 cm² in the control group (p-value = 0.012). After dressings, the mean area of granulation tissue formation in the study group was 39.63 cm² ± 2.6, while it was 36.07 cm² ± 5.7 in the control group (p-value = 0.001*). The control group's average hospital stay was 31.3 ± 4.2 days whereas in the study group it was 27.8 ± 2.4 days (p-value = 0.001*). **Conclusion:** Insulin is a cheap and superior alternative dressing agent for diabetic foot ulcer care.

KEYWORDS

Granulation Tissue, Hospital Stay, Surface Area, Dressing Agent

INTRODUCTION:

Chronic wounds, especially the non-healing type, are one of the most common conditions encountered by a surgeon. The peculiarity of chronic wounds is that, despite daily dressings with expensive local applications, the wound does not heal. The problem is especially seen in diabetic ulcers^[1-4], venous ulcers and pressure ulcers^[5]. It is estimated that 19–34% of patients with diabetes are likely to be affected by diabetic foot ulcers in their lifetime^[6]. Diabetic foot ulcers (DFUs) are the most common cause of hospitalization in patients with Diabetes Mellitus. The etiology of DFUs is multifactorial. The major underlying causes are peripheral neuropathy and ischemia from peripheral vascular disease. Other factors include trauma, deformity, callus formation, and oedema^[7,8]. To treat these wounds is a constant challenge for the surgeon.

At present, continuous research is going on for the development of expensive topical growth factors for wound healing. Thus, there remains a quest for better wound healing agents. One such agent is Insulin, which is cheap, easy to use and readily available. Insulin was initially introduced for the treatment of type-1 and uncontrolled type-2 Diabetes Mellitus. The use of insulin for non-diabetic purposes was popular in the early 20th century^[9,10], was overlooked in the 40's and 50's and was revived in the second half of the century. For instance, daily insulin injections were used to speed up the healing of wounds in horses^[11], mice^[12] and rats^[13,14,15,16]. Human diabetic wounds were also treated with insulin in the 1960s^[17,18], and more recently, insulin spray has been used to successfully treat individuals with diabetes ulcers. In addition to the in vivo investigations, research using cultured cells has demonstrated that insulin accelerates the growth of fibroblasts, cells

essential for the formation of the granulation tissue^[19], indicating that insulin can function as a growth hormone^[20]. Although the exact mechanism of action is not clearly understood, the postulated mechanisms of action of insulin in wound healing are:

- Stimulation of Keratinocyte migration and differentiation independent of EGF.^[21,22,23]
- Inhibition of Apoptosis through Insulin like growth factor-1 (IGF-1)^[22]
- Proliferation of myofibroblasts resulting in collagen synthesis and production of components of extracellular matrix^[22,23,24,25]
- Promotes macrophage activation^[23]

Important step in managing diabetic ulcer is offloading the wound by using appropriate therapeutic footwear, daily saline dressings or similar dressings to provide a moist wound environment, debridement whenever necessary, antibiotic therapy, optimal control of blood glucose, evaluation and correction of peripheral vascular insufficiency. Numerous topical medications and gels are being promoted for ulcer care and healing. However relatively few have proved to be more efficacious than saline dressings. Normal saline is a non-irritant, physiological and isotonic solution. It acts by clearing away the cellular debris, reducing the tissue edema, and thus preparing the wound bed for further management. Hence the present study was undertaken to compare the effect of topical insulin and normal saline dressings in healing of diabetic foot ulcers and also to document any local or systemic side effects with the usage of topical insulin.

OBJECTIVE:

To determine the efficacy of topical insulin dressings and compare

with conventional saline dressings in the healing of diabetic foot ulcers in terms of: Mean area of granulation tissue formation, Duration of hospital stay, Effect on bacterial load and adverse effects if any.

MATERIALS AND METHODS:

This study was a prospective longitudinal study that was approved by our Institutional Ethics Committee bearing serial number 373/IEC AMC/NOV 2021. The study included 100 patients with chronic diabetic foot ulcers admitted to a tertiary care hospital, King George Hospital affiliated with Andhra Medical College of North Andhra Pradesh from August 2021 to July 2022 for a period of 1 year after obtaining informed consent from all the patients.

Inclusion Criteria:

Patients with diabetic foot ulcers of chronic duration (≥ 3 months). Diabetic patients between the cohort of 30 and 80 years. Patients who have ulcers measuring over one cm^2 over lower leg and foot. Patients with glucose levels between 110 and 130 gm/dl. Patients with grade I and II ulcers of Wagner's classification¹⁸ and patients who gave a legit consent for participation.

Exclusion Criteria:

Patients who were unwilling to participate in the study. Patients who were below the age of 25 years. Ulcers which were related to osteomyelitis, tuberculosis and malignancy. Patients who were seropositive and having other comorbid conditions like renal failure, and generalized debility which adversely affects wound healing and patients known to be allergic to insulin were excluded.

The study population was divided into two groups based on the patient's willingness for undergoing topical insulin therapy for the wound. Patients who were not willing to take up the insulin dressings were subjected to traditional saline dressings which formed the control group and patients who were willing to undergo the topical insulin dressing therapy formed the study group. The wounds were thoroughly debrided where ever necessary. Pus culture and sensitivity studies were done for both study and control group patients and antibiotic therapy was advocated accordingly. The patients were subjected to X-rays to rule out the presence of osteomyelitis. After slough removal, the ulcer surface area was determined through mechanical planimetry by multiplying the two maximal perpendicular diameters of the ulcer, and it was expressed in square centimeters (cm^2).

Saline is used to clean wounds in the study group and then for each 10 cm^2 surface area of the wound, 5 ml of normal saline mixed with 10 IU of regular insulin is used. A sterile gauge is soaked in this solution and placed over the wound and dressing done. The traditional dressing was done with sterile surgical pad soaked with saline solution at 5ml/ cm^2 . Both the group patients were followed up daily for 14 days. At the end of 14 days, the extent of the ulcer area in both the control and study groups were inspected and compared based on the following parameters: Granulation tissue formation as a percentage of ulcer's extent (surface area) and duration of hospital stay. The granulation tissue formed at the end of 14 days was measured through mechanical planimetry by multiplying the two maximal perpendicular diameters of the granulation tissue formed, and it was expressed in square centimeters (cm^2). If in case the granulation tissue formed was patchy or if there was a non healing part of ulcer in between the granulation tissue formed, the ulcer was divided into multiple parts and area of each part is calculated separately and added excluding the non healed area. This measurement was done twice and if both the values are identical then it is taken into consideration and if not, the mean of two values is taken into account. Then the percentage of ulcer area at the beginning of study that is covered with granulation tissue at the end of study was calculated.

Statistical Analysis:

The data obtained were evaluated statistically, and the results were analyzed using Microsoft excel 2016 version. The variables in both the groups were compared using Paired and Unpaired Student's t-test. P value < 0.05 was considered significant.

RESULTS:

It was observed that there were 42 males and 8 females in the study group and 37 males and 13 females in the control group. The male to female ratio in the study group was 5:1 and in the control group was 3:1. The mean age in the study group was $53.94 \text{ yrs} \pm 9.26$ and the mean age in the control group was $55.92 \text{ yrs} \pm 7.98$. The number of cases with

grade-1 ulcer were 14 in the study group and 17 in the control group whereas the number of cases with grade-2 ulcer were 36 in study group and 33 in control group.

The mean ulcer surface area in the control group was 37.6 cm^2 and in the study group was 40.4 cm^2 . The efficacy of the dressing was assessed as the percentage of ulcer surface area covered by healthy granulation tissue after 14 days. The mean area of granulation tissue formation in the control group was $36.07 \text{ cm}^2 \pm 5.7 (\text{SD})$ and in the study group was $39.63 \text{ cm}^2 \pm 2.6 (\text{SD})$ of the total ulcer surface area. The mean of percentages of area of granulation tissue formation in the control group was 95.91% of total ulcer surface area and in the study group was 98.09% of total ulcer surface area. The p-value is 0.001*, which is significant.

Table 1: Ulcer Surface area

Group	Mean $\pm$ SD (cm ²)	Median (cm ²)	t-value	p-value
Saline	37.60 $\pm$ 7.22	38.6100	2.548	0.012*
Insulin	40.40 $\pm$ 2.84	40.2200		Significant
Total	39 $\pm$ 5.6	39.7100		

Table 2: Area of Granulation tissue formation

Group	Mean $\pm$ SD (cm ²)	Median (cm ²)	t-value	p-value
Saline	36.071 $\pm$ 5.7160	37.060	3.996	0.001*
Insulin	39.63 $\pm$ 2.6753	39.650		
Total	37.855 $\pm$ 4.7881	38.985		

The mean hospital stay in the control group was 31.3 ± 4.2 days and that in the study group was 27.8 ± 2.4 days (p value = 0.001*)

Table 3: Duration of Hospital Stay

Group	Mean $\pm$ SD (days)	Median (days)	t-value	p-value
Saline	31.30 $\pm$ 4.200	30.00	4.992	0.001*
Insulin	27.88 $\pm$ 2.413	28.00		
Total	29.59 $\pm$ 3.817	28.50		

The most common organisms isolated in our study group were *E. Coli* - 15, *Pseudomonas* - 14, followed by *Klebsiella* - 11, *Staphylococcus* - 3. The culture was sterile in 07 patients whereas in our control group the most common organisms isolated were *E. Coli* - 12, *Pseudomonas* - 13, *Klebsiella* - 11, *Staphylococcus* - 06 and *Streptococcus* - 01. The culture was sterile in 07 patients in control group. The treatment with antibiotics was based on the pus culture and sensitivity reports.

In both the groups, no side-effects or complications occurred during the hospital stay. The patients were followed up after one month of discharge for any complications. No further complications were noted at follow-up.



Figure 1: Ulcer before insulin dressing



Figure 2: Ulcer after insulin dressing

DISCUSSION

Wound dressings have evolved from the status of providing physical protection to the raw surface, absorbing exudates and controlling local

infections by local medications to the level of providing an adequate environment and promoting wound healing. This has been achieved by modern wound dressing agents which promote granulation tissue formation^[26]. Insulin is one such promising agent which still requires extensive research for its application in chronic Diabetic foot ulcers.

Insulin dressings in chronic Diabetic Foot Ulcers which is an area of interest because of their low tendency for healing which poses a challenge for the researchers worldwide.

In the present study, the mean age in the study group was 53.94 years and in the control group was 55.92 years. The results were similar to a study by Biradaret al.^[27] (2020), in which the mean age was 51.20 years in insulin group, while 50.60 years in the conventional group. Our results were similar another study conducted by Noura Mahmoud Elrefaey et al.^[28] (2019) who identified the mean age in the study group to be 51.53 years and in the control group to be 52.60 years. Dr. Vijay V Kamat et al.^[29] (2018) observed that the mean age of study group was 47.80 years and that of control group was 59.40 years. Their observations were slightly lower than the mean age of our study in study group and higher than mean age of study in control group.

In our study population, males outnumbered females which was similar to the findings of Dr Pandey Sanjay et al.^[30] (2015), Thakur PB et al.^[31] (2019) and R. Swaminathan^[32] (2013). This is in contrast to the study conducted by Shafaatullah et al.^[33] (2016), where females outnumbered the males.

The amount of good granulation tissue is a major indicator of healthy healing. The mean granulation tissue formation as a percentage of surface area of ulcer in the saline dressing control group is 95.93% of total ulcer surface area and in the insulin dressing study group is 98.09% of total ulcer surface area. These results were similar to studies by Dr Pandey Sanjay et al.^[30] (2015), Dr. Vijay V Kamat et al.^[29] (2018), Sreelesh P V et al.^[34] (2018) and Shafaatullah et al.^[33] (2016) which revealed similar observations.

The mean hospital stay in the insulin dressings study group was 27.8 ± 2.4 days and in the saline dressings control group was 31.3 ± 4.2 days. The mean hospital stay of the total patient-population is 29.6 ± 3.8 days. Our results were comparable to the results of studies conducted by Dr Pandey Sanjay et al.^[30] (2015) and Goenka G et al.^[35] whose hospital stay in their study groups were 21.1 ± 4.4 days and 40.1 ± 16.6 days respectively.

There were no adverse effects observed to topical insulin dressings in our study. These findings were in correlation with those observed by Goenka G et al.^[35] (2012) and Rasha Hassan Abass Shady et al.^[36] (2018) who did not report any reactions.

Table 4 : Comparison of the length of hospital stay among various studies

Studies	Average length of hospital stay (in days)	
	Study	Control
Present study	27.8 ± 2.4	31.3 ± 4.2
Dr Pandey Sanjay et al. ^[30] (2015)	21.0 ± 4.4	25.9 ± 4.3
Goenka G et al. ^[35] (2012)	40.1 ± 16.6	46.2 ± 17.9

Limitations:

The most important limitation of this study is its sample size and that it is not a randomized control study. The follow-up period was short. A randomized controlled study with a larger sample and longer follow-up period may help to further substantiate the findings or reveal variations that were not observed in the present study.

CONCLUSION:

The variables of the surface area of ulcer, granulation tissue formation, and duration of hospital stay studied revealed that topical insulin dressings were superior to traditional saline dressings in the management of chronic diabetic foot ulcers. There were no side effects either to topical insulin dressings or conventional saline dressings during hospital stay or during the follow-up period. Insulin may be a cheap and better alternative dressing agent for diabetic foot ulcer care.

Conflict Of Interest: none

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