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THE EFFECTIVENESS OF TOPICAL INSULIN DRESSING IN MANAGEMENT OF CHRONIC DIABETIC FOOT ULCER

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Abstract

Background: Topical insulin improves wound healing by regulating oxidative and inflammatory responses. Administration of the topical insulin in the dressings enhances keratinocyte migration, catalyses angiogenesis, stimulates microvascular endothelial cell migration and endothelial tube formation, accelerates re-epithelialization, and increases fibroblastic reaction. In spite of insulin therapy and a strict adherence to diabetic diet, nearly 15% of all diabetic patients will experience non-healing lesions, which is the main reason for lower extremity amputation. **Objectives:** To study the effectiveness of topical insulin in the management of patients with chronic diabetic foot ulcer. **Methodology:** This is a Randomized Control trail, 24 patients with chronic diabetic foot ulcer, treated under the Department of General Surgery, Thiruvarur Medical College, divided into Study group/ Group A/ Topical Insulin Group consisted of 12 adult patients who received topical insulin dressing and Control group/ Group B/ normal saline group consisted of 12 adult patients, who receive normal saline dressing. Ulcer size and healing was recorded on weekly basis. Strict glycemic control was maintained in all diabetic patients. Culture and sensitivity were done every week. **Results:** Age, gender, size of the ulcer, fasting blood sugar, postprandial sugar, area of the ulcer, were not significantly different between the groups received topical insulin and normal saline dressing. The mean Healing Time (in Days) and Time for no Growth in Culture is significantly lower among the topical insulin group compared to the normal saline dressing group. 100% of the Group A group were Cured, whereas in Group B 91.66% were Cured and 8.33% were Lost follow up and the difference was not statistically significant. The outcomes within age and gender, among the groups were not statistically significant. **Conclusion:** Healing Time and Time for no Growth in Culture is significantly lower among

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the topical insulin group. Since, topical insulin is easily available, simple to administer and can be cost-effective in the management of diabetic ulcer.

Keywords: Topical insulin, management of chronic diabetic foot ulcer, diabetic foot, diabetic foot ulcer.

Introduction

Prevalence of diabetes mellitus, especially type II Diabetes mellitus, is increasing globally in the past few decades, and more aggressively in the Indian scenario. This is due to changes in the lifestyle, rapid industrialisation, and increase in the prevalence of risk factors such as changes in diet, exercise, smoking, alcoholism, obesity, sleep, and stress. Diabetes remains as one of the significant causes of the morbidity, disability, and mortality.

Among the diabetic population, foot complications are a major cause of morbidity, hospitalisation, disability, mortality and decrease in quality of life. 25% of diabetics develop some foot problems during their illness. Risk factors for Diabetic foot ulcer include, longer diabetes duration, associated peripheral neuropathy, peripheral vascular diseases, previous foot ulcers and amputations.

The prevalence of chronic ulcers in India has been reported as 4.5 per 1000 population. About 50% of the patients affected with diabetic foot ulcers need a minor or major lower limb amputation. About 45% of all lower limb amputations are performed due to the Diabetic foot disease. After the amputation of the limb, the 5-year survival rate of the patients is only about 30%.

Wound healing is a complex biological process. Several factors, including human acidic fibroblast growth factor (HAFGF) and insulin-like growth factor (IGF), have an impact on the biological process of wound healing (rh-aFGF). IGF has been demonstrated in vivo studies to increase endothelial cell proliferation and differentiation, promoting the regeneration of granulation tissue and aiding in wound healing.

Wound healing is promoted and improved by regulating oxidative and inflammatory responses by topical insulin. Administration of the topical insulin in the dressings enhances keratinocyte migration, catalyses angiogenesis, stimulates microvascular endothelial cell migration and endothelial tube formation, accelerates re-epithelialization, and increases fibroblastic reaction.

Need for the study / Justification of the study:

Despite insulin therapy and a strict adherence to diabetic diet, nearly 15% of all diabetic patients will experience non-healing lesions, which is the main reason for lower extremity amputation. Topical insulin is easily available, simple to administer and can be cost-effective in the management of diabetic ulcer. There are very few studies in this topic, particularly in the Indian context. Therefore, the aim of this prospective, randomised study was to determine the effectiveness and safety of topical insulin for treating patients with persistent diabetic ulcers.

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Aim and Objectives

Aim

- To study the effectiveness of topical insulin in management of patient with chronic diabetic foot ulcer.

Objectives

I. Primary Objectives:

- To study the effectiveness of topical insulin in management of patient with chronic diabetic foot ulcer in following terms, with the rate of wound healing, safety evaluation and duration of hospital stay.

II. Secondary Objectives:

- To compare the efficacy of topical insulin with that of a control group using conventional saline dressings, in the healing of diabetic ulcers in terms of number of days needed for healing and rate of reduction in mean ulcer surface area
- To assess the effect of topical insulin in bacterial load by comparing the culture and sensitivity of wound swabs before and after application of insulin

Methodology

Study Subjects:

24 patients with chronic diabetic foot ulcer, treated under the Department of General Surgery, Thiruvarur Medical College.

Study Design:

Randomized Control trail.

Study Period:

Data collection – 1 year (May 2021 to May 2022).

Study setting:

Department of General Surgery, Thiruvarur Medical College.

Sampling Procedure:

Purposive Sampling, with random allocation of interventions.

Inclusion Criteria:

- Patients willing to give informed consent,
- All patients admitting with history suggestive of chronic diabetic ulcers,
- Age group of 25 years to 75 years,
- Grade 1 and Grade 2 ulcer (Wagner's classification),
- Patients having diabetic ulcers measuring greater than one cm.

Exclusion criteria

- Ischaemic limb,
- Age more than 75 years,
- Patients with malnutrition, immunodeficiency,
- Non-complying patients who do not provide consent to participate in the study,
- Patients who were not on regular follow-up.

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6. Sample Size ESTIMATION

According to **Paritosh singh B. Thakur *et al.*** study, considering the mean and standard deviation of Average time required for granulation tissue to appear in topical insulin group as 5.68 ± 2.45, mean and standard deviation of Average time required for granulation tissue to appear in normal saline group as 8.97 ± 3.29 at 95% confidence interval with 80% power, the sample size is calculated as

$N = (Z1-\alpha/2 + Z1-\beta)2 * 2 * \sigma2/ (\mu1 - \mu2)2$

$Z1-\alpha/2$ - two tailed probability for 95% confidence interval = 1.96

$Z1-\beta$ - two tailed probability for 80% power = 0.84

$\mu1$ - mean of Average time required for granulation tissue to appear in topical insulin group = 5.68

$\mu2$ - mean of Average time required for granulation tissue to appear in normal saline group = 8.97

σ - average standard deviation of Average time required for granulation tissue to appear in topical insulin group & Average time required for granulation tissue to appear in normal saline group = 2.87

N = (1.96 + 0.84) ^2 * 2 * 2.87^2 / (5.68 - 8.97) ^2

N = 11.95

Thus the sample size required for each group is 12 and the total sample size is 24

Ethical Consideration:

Institutional Ethical Committee approval, from Thiruvarur Medical College, was obtained before the start of the study. Informed written consent was obtained.

Study procedure:

All thepatients who were satisfying inclusion/ exclusion criteria were randomized into two groups, Group A and Group B. A detailed history, and a thorough clinical examination were done followed by the complete blood and imaging investigations. The data was entered in pre-structured study proforma.

Study group: consisted of 12 adult patients who receive topical insulin dressing.

Control group: consisted of 12 adult patients, who receive normal saline dressing

Group A patients were treated with insulin dressings and Group B patients ulcers were treated with normal saline dressings. Ulcer size and healing was recorded on weekly basis. Strict glycaemic control was maintained in all diabetic patients. Culture and sensitivity were done every week.

Results were compared at complete healing or at the end of 4 weeks which ever was earlier.

The following algorithm represents the CONSORT flow diagram representing steps involved in the study procedure

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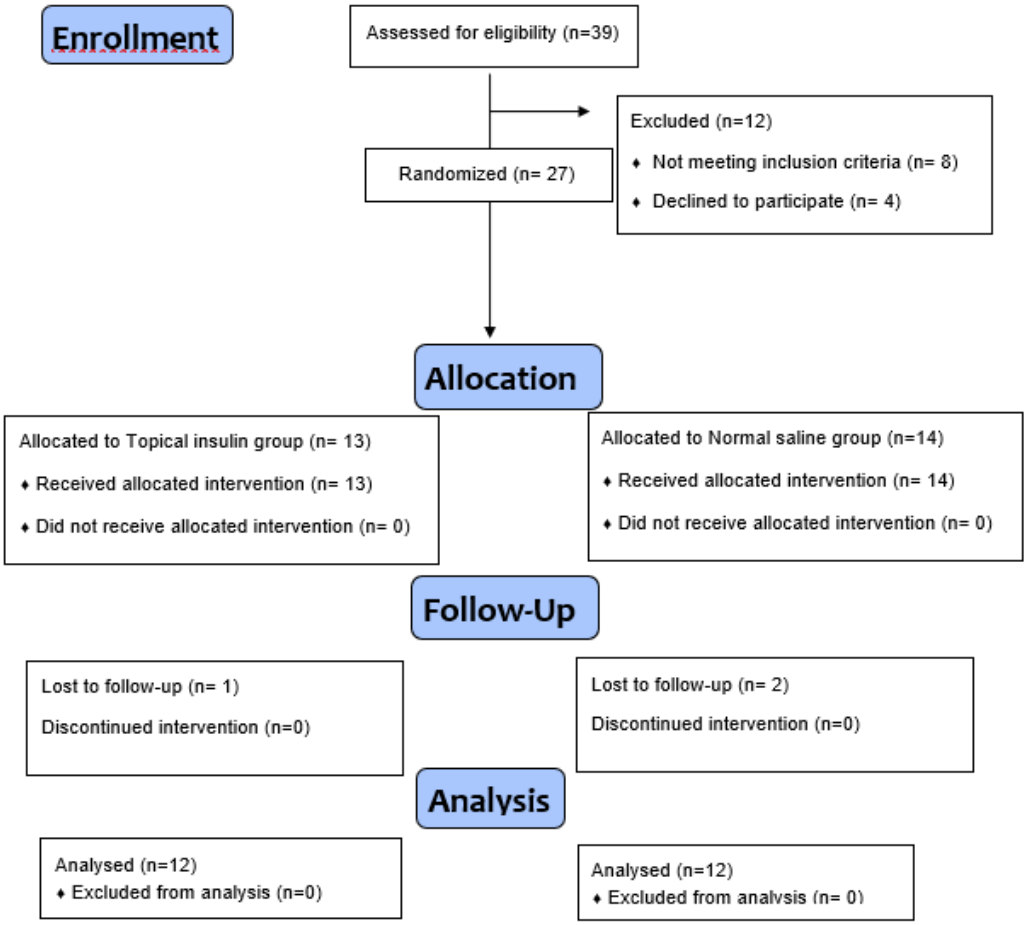

Statistical Methods

I. Descriptive Statistics

1. Numerical variables like Age, number of days needed for healing, duration of hospital stay, etc., are represented in mean, SD, median, and mode. Histograms are used wherever necessary.

2. Categorical variables like gender, study groups, side-effects, etc., are represented in frequencies and percentages. Pie-charts and bar diagrams are used as appropriate.

3. Data was entered in MS excel sheet and analysed using SPSS software version 16.

II. Inferential Statistics

1. When a Numerical variable is compared between the topical insulin and normal saline group, independent t test is used.
2. When a Categorical Variable is compared between the topical insulin and normal saline group, the variables are represented in both by tables and bar diagrams. For test of significance, chi-square test is used.
3. P-values lesser than 0.05 level were considered statistically significant.

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Observations And Results

Study groups: The study population comprise of 24 patients with chronic diabetic foot ulcer, divided into Study group/ Group A/ Topical Insulin Group consisted of 12 adult patients who received topical insulin dressing and Control group/ Group B/ normal saline group consisted of 12 adult patients, who receive normal saline dressing.

Age: The mean Age among Group A was 55.58 (± 7.67) which is lower by 4.42 but not statistically significant compared to 60 (± 9.41) in Group B. Group A group had higher proportion of 51 - 60 years with 50%, compared to Group B group which had higher proportion of 51 - 60 years with 33.3%. The difference in Age group distribution between Group A and Group B was not statistically significant ($p > 0.05$).

Gender: 41.66% of the Group A group had Males and 58.33% had Females compared to Group B group of whom 75% had Males and 25% had Females and the difference was not statistically significant ($p > 0.05$).

Ulcer Foot – Side: 58.33% of the Group A group had Left side and 41.66% had Right side compared to Group B group of whom 75% had Left side and 25% had Right side and the difference was not statistically significant ($p > 0.05$).

Culture organisms: The most common organism isolated was Klebsiella, followed by Staphylococcus, mixed flora, enterococci, candida.

FBS (mg%): The mean FBS (mg%) among Group A was 258.33 (± 75.65) which is lower by 4.5 but not statistically significant compared to 262.83 (± 76.71) in Group B.

PPBS (mg%): The mean PPBS (mg%) among Group A was 336.58 (± 47.94) which is higher by 3.58 but not statistically significant compared to 333 (± 76.77) in Group B.

Ulcer area: The mean Ulcer area baseline among Group A was 45.17 (± 33.33) which is lower by 0.17 but not statistically significant compared to 45.33 (± 31.07) in Group B.

Healing Time (Days): The mean Healing Time (Days) among Group A was 37.08 (± 7.89) which is lower by 19 and statistically significant compared to 56.08 (± 9.41) in Group B.

Table 1: Healing Time (Days) with Group

	Group	**N**	**Mean**	**Std. dev.**	**Mean diff.**	**p value by 't' test**
Healing Time (Days)	**Group A**	12	37.08	7.89	19.00	0.001
	Group B	12	56.08	9.41		

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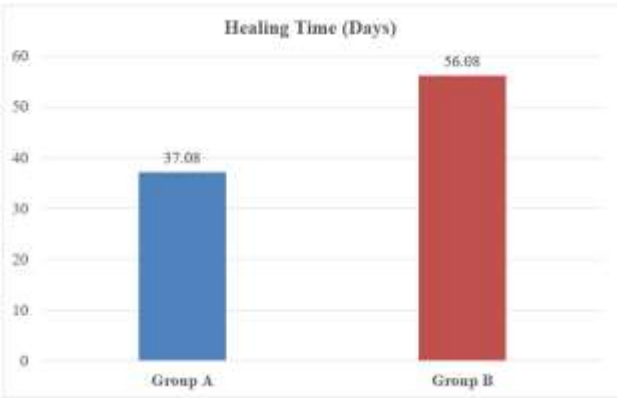

Figure 1: Healing Time (Days) with Group

Time for NIL Growth in Culture: The mean Time for NIL Growth in Culture among Group A was 9.67 (± 3.68) which is lower by 17.83 and statistically significant compared to 27.5 (± 3.58) in Group B. The mean Time for NIL Growth in Culture among age groups, both the genders, within the groups were not statistically significant.

Table 2: Time for NIL Growth in Culture with Group

	Group	N	Mean	Std. dev.	Mean diff.	p value by 't' test
Time for NIL Growth in Culture (days)	**Group A**	12	9.67	3.68	17.833	0.001
	Group B	12	27.50	3.58		

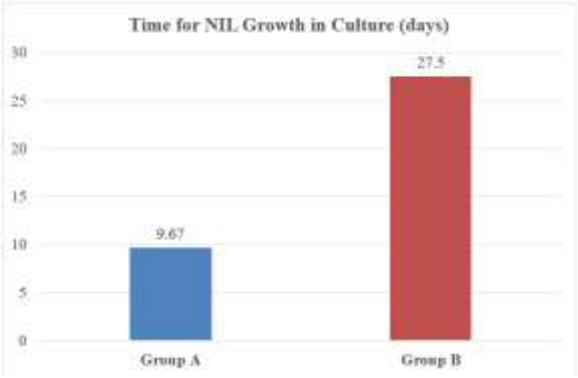

Figure 2: Time for NIL Growth in Culture with Group

Comparison of Outcome with the Group: 100% of the Group A group were Cured and 0% were Lost follow up compared to Group B group of whom 91.66% were Cured and 8.33% were Lost follow up and the difference was not statistically significant ($p > 0.05$)

Comparison of age with outcomes: Comparison of age group, with the healing time and Time for no Growth in Culture between the Groups was not statistically significant.

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Comparison of gender with outcomes: Comparison of gender, with the healing time and Time for no Growth in Culture between the Groups was not statistically significant.

Discussion

Topical insulin improves wound healing by regulating oxidative and inflammatory responses. Administration of the topical insulin in the dressings enhances keratinocyte migration, catalyses angiogenesis, stimulates microvascular endothelial cell migration and endothelial tube formation, accelerates re-epithelialization, and increases fibroblastic reaction.

Despite insulin therapy and a strict adherence to diabetic diet, nearly 15% of all diabetic patients will experience non-healing lesions, which is the main reason for lower extremity amputation. Topical insulin is easily available, simple to administer and can be cost-effective in the management of diabetic ulcer.

Age

All stages of wound healing are slowed down in the elderly, even though they can usually heal most wounds. Both the proliferative response and the inflammatory response are slowed down or delayed. Remodeling happens, but to a lesser extent, and the collagen produced is of a different quality.

In this study, the mean Age among Group A was 55.58 (± 7.67) which is lower by 4.42 but not statistically significant compared to 60 (± 9.41) in Group B. Group A group had higher proportion of 51 - 60 years with 50%, compared to Group B group which had higher proportion of 51 - 60 years with 33.3%. The difference in Age group distribution between Group A and Group B was not statistically significant ($p > 0.05$).

In this study, Comparison of age group, with the healing time and Time for no Growth in Culture between the Groups was not statistically significant. Hence the role of confounding bias by age on the study results can be eliminated.

Gender

One of the high-risk variables for poor healing of venous ulcers was male gender. (56,57) In this study, 41.66% of the Group A group had Males and 58.33% had Females compared to Group B group of whom 75% had Males and 25% had Females and the difference was not statistically significant ($p > 0.05$).

Elisabetta Iacopi *et al.*, in their study observed among diabetic foot ulcers, Men had a significantly higher healing rate, but a longer healing time, compared with women.

In this study, Comparison of gender, with the healing time and Time for no Growth in Culture between the Groups was not statistically significant. Hence the role of confounding bias by gender on the study results can be minimal.

Ulcer Foot – Side:

In this study, 58.33% of the Group A group had Left side and 41.66% had Right side compared to Group B group of whom 75% had Left side and 25% had Right side and the difference was not statistically significant ($p > 0.05$).

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Culture organisms

Klebsiella pneumoniae, Staphylococcus aureus and coagulase negative staphylococci are the common organisms isolated from the diabetic foot ulcers in various studies. In this study, the most common organism isolated was Klebsiella, followed by Staphylococcus, mixed flora, enterococci, candida.

Glycemic control

Poor glycemic control indicated by the higher HbA1C and fasting blood sugar are linked to a poor healing rate and a higher risk of amputation in patients with diabetic foot ulcers. (62–64)

FBS (mg%): In this study, the mean FBS (mg%) among Group A was 258.33 (± 75.65) which is lower by 4.5 but not statistically significant compared to 262.83 (± 76.71) in Group B.

PPBS (mg%): In this study, the mean PPBS (mg%) among Group A was 336.58 (± 47.94) which is higher by 3.58 but not statistically significant compared to 333 (± 76.77) in Group B.

Ulcer area

In this study, the mean Ulcer area baseline among Group A was 45.17 (± 33.33) which is lower by 0.17 but not statistically significant compared to 45.33 (± 31.07) in Group B. This ensures a baseline comparability between the groups.

Healing Time (Days)

In this study, the mean Healing Time (Days) among Group A was 37.08 (± 7.89) which is lower by 19 and statistically significant, when compared with group B 56.08 (± 9.41).

Like our study results, **Paritosh Singh B. Thakur *et al.***, observed that the Average time required for granulation tissue to appear, average surface area of wound and average depth of the wounds at day 6th day were significantly lesser among the topical insulin group as compared to the normal saline group.

In our study we did not observe any significant side-effects among both the groups. **R. Swaminathan *et al.***, observed that the average surface area of wound and average depth of the wounds were significantly lesser among the topical insulin group as compared to the normal saline group, without any side effects. **Jiao Wang *et al.***, concluded from their review, that the topical insulin has improvement in wound healing through various mechanisms without causing side effects.

Time for NIL Growth in Culture

In this study, the mean Time for NIL Growth in Culture among Group A was 9.67 (± 3.68) which is lower by 17.83 and statistically significant compared to 27.5 (± 3.58) in Group B. The mean Time for NIL Growth in Culture among age groups, both the genders, within the groups were not statistically significant.

Zhaoxin Zhang *et al.*, observed that the Growth of granulation tissue, presence of new vessels and micro vessel vascularisation was significantly higher among the insulin group compared with the control group, but with significant reduction in the systemic blood glucose levels. **Mehreen K Bhettani *et al.***, observed that the average size of wound was significantly lesser among the topical insulin group as compared to the normal saline group.

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Maria H M Lima *et al.*, observed that the Expression of IR, IRS-1, IRS-2, SHC, ERK, and AKT are elevated in the tissue of healing wounds compared to intact skin, with significant decrease in wound healing time, indicating that the insulin signalling pathway may have a vital role in the wound healing process.

Comparision of Outcome with the Group

In this study, 100% of the Group A group were Cured and 0% were Lost follow up compared to Group B group of whom 91.66% were Cured and 8.33% were Lost follow up and the difference was not statistically significant ($p > 0.05$) like our study results, **Kannan Sridharan *et al.***, observed that the pooled estimates revealed a healing rate; percent granulation tissue, and micro vessel density (Except for wound area), were not significantly affected with the usage of topical insulin.

In our study, we did not focus on the quality of life among the study participants. **Enas A S Attia *et al.***, observed that significantly greater quality of life scores and improved healing of ulcers, among the topical crystalline insulin group and aqueous zinc solution group as compared to the control group. Among the two groups, topical crystalline insulin group was having better results than the aqueous zinc solution group. They further observed that the healing was good in acute wounds and upper body wounds.

In our study, the study participants were followed up on OP basis, so could not study the duration of hospital stay. **Gaurav Goenka *et al.***, observed that the rate of wound healing and hospital stay were significantly lesser among the topical insulin group as compared to the normal saline group, without any side effects.

Conclusion

Age, gender, side of the ulcer, fasting blood sugar, postprandial sugar, area of the ulcer, were not significantly different between the groups received topical insulin and normal saline dressing. The mean Healing Time (in Days) and Time for no Growth in Culture is significantly lower among the topical insulin group compared to the normal saline dressing group.

100% of the Group A group were Cured, whereas in Group B 91.66% were Cured and 8.33% were Lost follow up and the difference was not statistically significant. The outcomes within age and gender, among the groups were not statistically significant.

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