Section: General Surgery

Original Research Article

EFFECT OF LOCAL INSULIN INJECTION ON WOUND HEALING IN DIABETIC FOOT ULCER

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ABSTRACT

Background: Objectives: To observe the „effect of local insulin injection on granulation tissue formation‟ and wound healing in patients with diabetic foot ulcer

Materials and Methods: Data was collected using a questionnaire, clinical examination and blood glucometer. Patients with diabetic foot ulcer were included for the study. Patients enrolled in this study were allocated to either the insulin group or the control group. All the patients underwent debridement of the diabetic foot ulcer on the day of start of study (D0) to remove any slough and unhealthy granulation tissue present. In the insulin group, one-half of the calculated dose of plain insulin was diluted with normal saline to a total volume of 1 ml and then injected diffusely into the base of the diabetic foot ulcer. The remaining half dose of insulin was subcutaneously injected into the abdominal wall. The insulin injections were performed twice a day. In the control group, the calculated dose of human insulin was subcutaneously injected into the abdominal wall and 1 ml normal saline subcutaneously injected into the base of the diabetic foot ulcer. The injections were performed twice a day. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance. Statistical analyses was performed by using a statistical software package SPSS, version 20.0.

Results: In this study, 84 „patients with diabetic foot ulcer‟ were assessed after dividing into two groups of 42 each – insulin group and control group. It was found that in the insulin group, where the patients received local and subcutaneous insulin injection, there was significant difference ($p < 0.01$) in growth of granulation tissue from as early as 5 days after local insulin injection. It was also noticed that there was no significant difference in fingertip blood glucose levels‟ between the two groups.

Conclusion: In conclusion, local injection of insulin into the base of a diabetic foot ulcer does seem to have a significant effect on the growth of healthy granulation tissue and hence improves wound healing, while having similar control in systemic blood glucose levels as the normal subcutaneous route of insulin injection.

Keywords: Diabetes mellitus, Diabetic foot ulcer, Local insulin injection, Healthy granulation tissue, Wound healing, Blood glucose levels.

INTRODUCTION

The prevalence of diabetes mellitus, a serious health issue, has skyrocketed in the last thirty years. Between 1980 and 2019, it has increased globally from 4.7% to 9.3%. According to WHO forecasts, India will have more than 300 million diabetics by 2025, making it the "Diabetic Capital of the World."

At some point throughout their condition, the majority of diabetic individuals experience foot ulcers. Diabetic foot complications like ulceration, infections, and gangrene are becoming more common in our surgical practice. Hospital stays become frequent and extended as a result. A large number of patients arrive at a stage where

significant amputations or even death are the outcome, as limb salvage is no longer an option.[1]

Diabetic foot‘ is a common complication of diabetes mellitus.[1] It is usually the result of poor glycemic control, underlying neuropathy, peripheral vascular disease, or poor foot care. In patients with diabetic foot ulcers, numerous factors can lead to the slow growth of the local wound granulation tissue, such as increased blood glucose (locally and systemically), inefficient wound angiogenesis and fibrous tissue deposition‖.[2]

Wound healing is the result of a complex series of reactions and interactions among cells and mediators. The principal steps in the process of wound healing are epithelization, angiogenesis, granulation tissue formation and collagen deposition.

The disorder and loss of function of angiogenesis in diabetic ulcer wounds are considered to be the dominating factors leading to poor wound healing‖.[3] At present, the key problems to be solved, for wound healing in patients are restoring the function and structure of the vasculature and improving.[4]

The biological effects of local insulin injection have been suggested to be associated with several molecular mechanisms. ―First, insulin reduces the local wound blood glucose concentration, thus reducing the damage resulting from the accumulation of high levels of glucose metabolic intermediates‖.[1] Secondly, insulin is the inhibitor of three major proinflammatory transcription factors: nuclear factor-κB,[5] activator protein-1 and early growth response-1 (EGR-1).[6] Furthermore, insulin enhances immune activity by inhibiting the degradation of immune cell proteins.[7]

Hence the aim of the present study was to observe the effect of local insulin injection on granulation tissue formation and wound healing in patients with diabetic foot ulcer.

MATERIALS AND METHODS

It was a Prospective Observational Study conducted for a period of 12 months (January 2023 to January 2024) in the Department of General Surgery, Govt. Medical College, Kottayam among Patients of diabetic foot ulcer treated in department of General Surgery, Govt. Medical College, Kottayam during the study period.

Sample Size

Calculated by the formula, n= (Zα+Zβ)2 x SD2
d2 n=SAMPLE SIZE

Zα = Z value at an α error = 1.96 at 95% CI Zβ = Z value at a β error =1.28 at 95% CI SD = Standard deviation = (SD1+SD2)/2

SD1 & SD2 are standard deviations of the two groups d= clinically relevant effect = (µ1-µ2)/2

n= (1.96 +1.28)2 x 0.42 = 42
0.22

42 in each arm = 84 patients in total

Study sample includes the patients of diabetic foot ulcer treated in the department of general surgery, Govt. medical college Kottayam, during the study period.

Granulation tissue growth = (Original wound area - wound area without granulation coverage)/original wound area x 100%.

Data was collected using a questionnaire, clinical examination and blood glucometer. Patients with diabetic foot ulcer were included for the study. Patients enrolled in this study were allocated to either the insulin group or the control group‘. All the patients underwent debridement of the diabetic foot ulcer on the day of start of study (D0) to remove any slough and unhealthy granulation tissue present.

In the insulin group, one-half of the calculated dose of plain insulin was diluted with normal saline to a total volume of 1 ml and then injected diffusely into the base of the diabetic foot ulcer. The remaining half dose of insulin was subcutaneously injected into the abdominal wall. The insulin injections were performed twice a day.

In the control group, the calculated dose of human insulin was subcutaneously injected into the abdominal wall and 1 ml normal saline subcutaneously injected into the base of the diabetic foot ulcer. The injections were performed twice a day.

Both groups received injections for 7 consecutive days. The wounds were also and cleaned with soap and water dressed daily, in both groups. In both groups, blood glucose levels were measured half an hour and 1 hr after insulin injection.

On days 0, 5, 7 12, 15 and 21 days after injection, wound healing was assessed in terms of healthy granulation tissue formation. The degree of granulation tissue growth was evaluated as follows. Briefly, prior to treatment, the original ulcer wound areas of the two groups were recorded using transparent tracing paper. The wound size was traced with the same method following treatment. The growth of the granulation tissue was calculated using the formula: Granulation tissue growth = (Original wound area - wound area without granulation coverage)/original wound area x 100%.

Inclusion Criteria

Patients of diabetic foot ulcer treated in department of General Surgery, Govt. Medical College, Kottayam during the study period.

Exclusion Criteria

1. Patients with other causes of foot ulcers - Peripheral vascular disease, varicose ulcer, malignant ulcer, amyloidosis, neuropathy
2. Patients who exhibit extensive and complete necrosis and required immediate amputation at the time of admission to hospital.
3. Age <18yrs

Statistical Analysis

Baseline sociodemographic characteristics and clinical findings were compiled as numbers and percentages. Data entry was done in MS Excel. Categorical and quantitative variables were

expressed as frequency (percentage) and mean ± SD. respectively. Independent t test was used to compare quantitative parameters between categories. Chi-square test was used to find association between categorical variables. For all statistical interpretations, p<0.05 was considered the threshold for statistical significance. Statistical analyses was performed by using a statistical software package SPSS, version 20.0.

RESULTS

Table 1: Age distribution of the study sample

Age	Control group		Insulin group	
	Count	Percent	Count	Percent
<50	6	14.3	5	11.9
50 - 59	18	42.9	15	35.7
60 - 69	15	35.7	19	45.2
>=70	3	7.1	3	7.1
Mean ± SD	58.4 ± 8.1		59.2 ± 8.1	

The mean age of study samples was 58.4±8.1 years in the control group and 59.2± 8.1 in the insulin group and it comprised of 29 (69%) males and 13 (31%) females in the control group and 28 (66.75) males and 14 (33.3%) females in the insulin group). It was found that mean duration of Diabetes was 8.4±4.7 years in the control group and 8.5±3.1 years in the insulin group. The mean duration of the diabetic foot ulcer was 2.9±1.5 months in the control group and 3.3±1.7 months in the insulin group.

Table 2: Comparison of Effectiveness of local insulin injection on growth of granulation tissue in the two groups

Growth of granulation tissue	Control group			Insulin group			t	p
	Mean	SD	N	Mean	SD	N		
D0	2.6	2.5	42	2.7	2.7	42	0.08	0.933
D5	17.6	3.4	42	19.9	4.4	42	2.67**	0.009
D7	29.6	4.5	42	33.0	6.3	42	2.82**	0.006
D12	39.5	5.6	42	47.0	5.8	42	6.01	p<0.01
D15	46.9	6.8	42	55.3	5.5	42	6.25	p<0.01
D21	53.4	11.4	42	61.0	19.0	42	6.86	p<0.01

****: - Significant at 0.01 level**

It was found that in the insulin group, where the patients received local and subcutaneous insulin injection, on the first day of receiving the local insulin injection (D0) there was no significant difference in the wound characteristics, in terms of area of healthy granulation tissue in both the groups (mean area of granulation tissue – 2.6 % in control group and 2.7 % in insulin group). However, there was significant difference (p < 0.01) in growth of healthy granulation tissue from as early as 5 days (D5) after local insulin injection between the two groups (mean area of healthy granulation tissue – 17.6% in control group and 19.9% in Insulin group). This difference was maintained and became more significant on further follow-ups on D7, D12, D15 and D21. On Day 21, the mean area of healthy granulation tissue was found to be 53.4 % in control group and 61.0% in insulin group with p value of <0.01, which shows there is a significant difference in growth of healthy granulation tissue between the two groups. It was seen that the patients who received local insulin injections into the diabetic foot ulcer developed healthy granulation tissue earlier than patients who did not and thus had better and enhanced wound healing.

Table 3: Comparison of fingertip blood glucose levels in the two groups, prior to and 0.5,1 and 2 hrs following insulin injection

Blood glucose	Control group			Insulin group			t	p
	Mean	SD	N	Mean	SD	N		
Prior	233.8	26.0	42	231.4	23.6	42	0.45	0.655
0.5 Hr	200.4	22.4	42	196.8	19.7	42	0.79	0.429
1 Hr	173.7	21.8	42	170.4	16.1	42	0.8	0.428
2 Hrs	149.9	19.4	42	142.5	15.3	42	1.92	0.058

In the study, fingertip glucose levels were measured in both the groups before giving insulin injections and 0.5, 1 and 2 hours after giving the insulin injections. It was noticed that there was no significant difference in fingertip blood glucose levels between the two groups. There was no significant difference in glycemic control achieved in both groups and there was hardly any need to hike insulin dosages in either group studied.

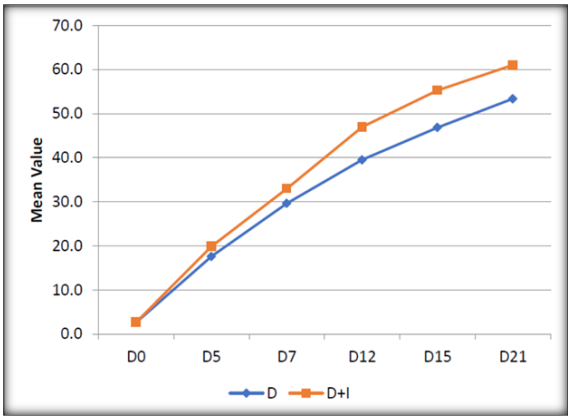

Figure 1: Mean Values Comparison

Graph showing comparison of healthy granulation tissue formation in patients receiving subcutaneous insulin alone (control group -D) and those receiving local as well as subcutaneous insulin injections (insulin group – D+I).

DISCUSSION

Local insulin injection has shown promise as an adjuvant therapy for diabetic foot ulcers (DFUs) in recent years, with potential benefits in enhancing wound healing. Previous research on the effectiveness of local insulin therapy has drawn a number of key findings. Insulin, being a potent anabolic hormone, regulates cellular metabolism, including glucose uptake and protein synthesis, all of which are essential for wound healing.

In addition to its many actions against platelet aggregation and atherosclerosis, insulin also protects the vascular endothelium, causes vascular dilation, and is cardioprotective.[5,8] It is reported that treating refractory diabetic wounds locally with insulin (local wet dressing or injection) is successful,[9] however, the results have been achieved in animal studies, and the insulin doses utilized lack a theoretical basis.[10] Therefore, it's unclear if local insulin use in humans is safe. Insulin wet packing struggles to produce the desired result because of obstructive variables like tissue necrosis, exudation from the wound surface, and low insulin permeability.[1] Insulin injected locally to a wound is more effective since it maintains a high concentration and longer duration of action.[1]

A study by Zhang Zi Xin et al demonstrated growth of granulation tissue in patients given local insulin therapy to be more exuberant from day 5, especially on day 7 [(59.06 ± 1.58) %] following intervention. This was significantly higher than that in the control group [(23.61 ± 1.57) %] They also observed neovascularisation in the intervention group as early as 3 days following local insulin injection, which was indicated by CD34 expression.[4]

Sridharan and Siva Ramakrishnan,[11] conducted a systematic review and meta- analysis as part of research on the effectiveness and safety of topical insulin delivery for the healing of wounds. The study found no evidence to support or refute the use of topical insulin in relation to the following outcomes: micro vessel density, granulation tissue growth percentage, and wound healing rate.

A randomized and controlled trial was conducted by Stephen et al,[12] to evaluate the impact of topical insulin versus normal saline on pressure ulcer healing. Comparing topical insulin to normal saline, they observed that their research showed a considerable increase in the rate of pressure ulcer healing.

Another study by Wang et al,[13] examined the effects of the local administration of high-dose insulin, low-dose insulin, and regular saline on wound healing following deep burn surgery. Insulin was discovered to be more effective at healing wounds than regular saline.

However, a study conducted by Mayurika Singh et al,[14] in 2022 showed equivocal results and they concluded that use of local insulin therapy is not the only factor that contributes to wound healing process in a diabetic foot ulcer. And that a combined approach including surgical wound debridement, treating infections, and proper care of wound is required for wound healing.

In the present study of 84 patients, there was found to be significant acceleration in growth of healthy granulation tissue and hence enhanced wound healing in patients with diabetic foot ulcers who received local insulin injection as compared to those who did not ($p < 0.01$). This difference was quantifiable from as early as 5 days after starting local insulin injections. The study also demonstrated that there was no significant difference in glycemic control between the insulin group and the control group.

In general, the available data indicates that local insulin injections can be very helpful in managing diabetic foot ulcers (DFUs) by accelerating wound healing, enhancing tissue regeneration, and lowering inflammation. These results provide credence to the inclusion of local insulin therapy in comprehensive diabetic foot ulcer treatment regimens. To thoroughly demonstrate the significance of local insulin in DFU therapy, future research should concentrate on optimizing treatment regimens and evaluating long-term effects.

Limitations

1. **Sample Size and Duration:** One limitation of this study is the sample size and duration of follow-up. A smaller sample may limit the generalizability of the findings, and a shorter study period may not fully capture long-term outcomes or potential delayed effects of local insulin therapy.
2. **Study Design:** The study design, whether it was a single-centre or multicentre trial, could affect the results. Single-centre studies might not account for variations in practice, patient demographics, and healthcare settings that can influence treatment outcomes.

3. **Measurement of Healing:** While the study effectively assessed granulation tissue formation and wound healing, the assessment methods (e.g., visual inspection, photographic analysis) may be subject to variability. Objective and standardized methods for measuring wound healing could improve result accuracy.
4. **Lack of Systemic Glucose Control Data:** Although systemic glucose levels were similar between groups, the study did not explore other metabolic parameters or potential side effects of local insulin therapy. Comprehensive metabolic assessments could provide a clearer understanding of the therapy's impact.
5. **Patient Variability:** The study may not account for patient variability, including comorbid conditions, medication adherence, and lifestyle factors, which can influence wound healing and overall treatment efficacy.

CONCLUSION

Our findings indicate that local insulin injections notably improve the formation of healthy granulation tissue and accelerate wound healing. This therapeutic strategy offers a targeted solution that addresses the chronic and challenging nature of DFUs. The absence of significant differences in blood glucose levels between the intervention and control groups highlights that the benefits of local insulin are likely due to its direct impact on the _wound healing‘ process rather than systemic glucose regulation.

The future implications of these findings are substantial. Local insulin injection presents a promising adjunctive therapy that could be integrated into standard DFU management protocols, offering a targeted approach to improve wound healing outcomes. The ability of local insulin to enhance granulation tissue formation and expedite wound closure suggests its potential to reduce healing time, minimize complications, and improve quality of life for patients with chronic diabetic ulcers. Overall, local insulin injections hold significant promise for improving DFU treatment, potentially transforming wound care practices and offering new avenues for managing diabetic complications effectively.

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