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Clinical Study of Local Application of Insulin on Diabetic Foot Ulcer Healing

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Abstract

Introduction: Foot complications are a major cause of hospitalization in patients with Diabetes Mellitus (DM), which consumes a high number of hospital days because of multiple surgical procedures and prolonged length of stay. Patients with DM have up to a 25% lifetime risk of developing a foot ulcer, which precedes amputation in up to 85% of cases. A mainstay of Diabetic Foot Ulcer (DFU) therapy is debridement of all necrotic, callus, and fibrous tissue, with a primary goal to obtain wound closure. **Materials and Methods:** Cases with diabetic foot ulcer presenting to our OPD/IPD and signing the informed consent form before study as well as fulfilling the inclusion criteria mentioned along with detailed clinical examination of the patient as well as laboratory workup the study was an open labelled randomised control trial. **Results:** The study was carried out with 64 patients selected randomly and sorted into two groups, i.e. the control and test subjects. No difference was observed in two groups with respect to wound depth after debridement (p-0.85). However, the depth of wound was significantly less in insulin group at week 1, 2 and 3 as compared to control group. The percentage decrease in wound depth was more in insulin group than control group by the end of 3rd week. Primary closure was observed in 62.5% and 84.4% patients while STSG was required in 37.5% and 15.6% cases of control and insulin group respectively.

Keywords: Amputation, Diabetes, Foot Ulcer, Insulin, Skin Graft

1. Introduction

Mainstay of Diabetic Foot Ulcer (DFU) therapy is debridement of all necrotic, callus, and fibrous tissue[1,2], with a primary goal to obtain wound closure. The management of the DFU is largely determined by its severity (grade), vascularity of the limb, and the presence of infection worsened by peripheral neuropathy[3–5]. In India, habits such as walking barefoot, lack of knowledge regarding diabetic foot, hot climate leading to increased perspiration, poor hygiene and sanitation, protein deficient diet, general poverty, lack of basic medical infrastructure, etc. have worsened the problem. Over the years the life expectancy of diabetic patient with gangrene of foot has not changed much. Advances in treatment of diabetes have caused increase in life span of diabetic patients which has resulted in an increase in complications of Diabetes Mellitus like vasculopathy, neuropathy and nephropathy. This in return has increased the prevalence and incidence of diabetic foot. The optimal topical therapy for DFU remains ill-defined. Saline-moistened gauze has been the standard method; however, it has been difficult to continuously maintain a moist wound environment with these dressings. Subsequently, various hydrocolloid wound gels, growth factors, enzymatic debridement compounds, hyperbaric oxygen therapy, cultured skin substitutes, and other wound management therapies have been advocated. All of these therapies are associated with significant expense and are being utilized in some situations without sufficient scientific evidence in favour of their efficacy[6]. Researches in past have shown that topical insulin accelerates wound healing in the skin of diabetic rats and humans[8-10]. Insulin locally stimulates the growth and development of different cell types and affects

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proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts[11,12].

2. Aims and Objectives

1. To study the efficacy of local application of insulin in promoting faster healing of Diabetic Foot ulcers, with faster reduction of size of ulcers & faster formation of healthy granulation tissue,
2. To study whether local insulin application causes faster preparation of ulcer bed for acceptance of a skin graft, and
3. To study whether local application of insulin causes a reduction in number of amputations in Diabetic Foot patients.

3. Materials and Methods

Using the formula of two independent means a total of 64 patients presenting with diabetic foot ulcers were included and randomly divided into one of the following two groups (32 each) using computer generated random numbers. The patients were screened, and glycaemic control was achieved along with detailed clinical examination and laboratory investigations including blood sugarand HbA1c levels respectively. The ulcer sizes were measured in terms of size and depth using wound planimetry and Q-tip method[14] for depth measurement then charted on a weekly basis for both groups to determine reduction in surface area, wound contraction and granulation.

3.1 Inclusion Criteria

1. All patients above 20 years of age with diabetic ulcer irrespective of Gender, type 1 or 2 diabetes mellitus, duration of diabetes,
2. Wagener grade 1 and 2 ulcers only, and
3. Newly diagnosed diabetic ulcer.

3.2 Exclusion Criteria

1. Patients not willing to participate,
2. Patients with established osteomyelitis, and
3. Patients with disorders which may impair wound healing (scurvy, zinc deficiency, also drugs which are cytotoxic or antineoplastic and immunosuppressive, NSAIDs andanti-coagulants).

4. Results

1. Mean age of study subjects was 53.6 and 53.1 years in control and insulin group respectively. The difference was statistically non-significant (p-1.0),
2. Male Preponderance was observed in both groups (87.5% in Control and 90.6% in insulin group respectively). The difference was statistically non-significant (p-1.0), and
3. No significant difference was observed on basis of grade of wound (p-0.79).

In about 78.1% of patients of insulin group, granulation tissue appeared by first week as compared to 53.1% in control group. By week 2 and 3, 90.6% and 96.9% cases in insulin group developed granulation tissue as compared to 68.8% and 75% in control group respectively. The difference was statistically significant (p<0.05 for all weeks) (Table 1 and Figure 1).

Table 1. Comparison of study groups as per development of granulation tissue

Granulation Tissue	Group		Total	p-value
	Control	Insulin		
Week 1	17	25	42	<0.05
	53.1%	78.1%	65.6%	
Week 2	22	29	51	<0.05
	68.8%	90.6%	79.7%	
Week 3	24	31	55	<0.05
	75.0%	96.9%	85.9%	

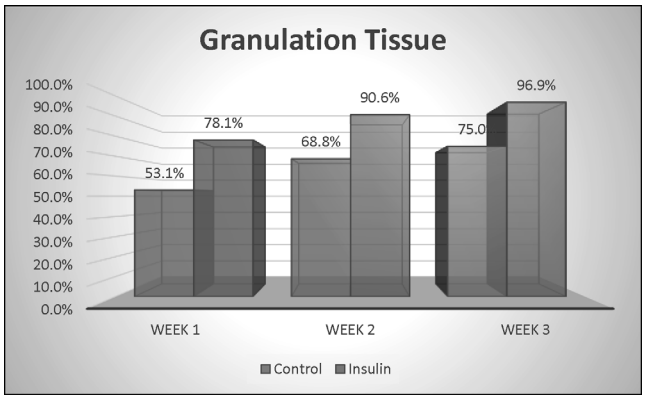

Figure 1. Granulation tissue (per week).

No difference was observed in two groups with respect to wound depth immediately after debridement (p-0.85). However, the depth of wound was significantly less in

insulin group at week 1,2 and 3 as compared to control group. The percentage decrease in wound depth was more in insulin group than control group by the end of 3rd week (51.66% Vs 42.6%; p<0.05). (Table 2 and Figure 2).

Primary closure was observed in 62.5% and 84.4% patients while STSG was required in 37.5% and 15.6% cases of control and insulin group respectively. No significant difference was observed in conventional and VAC group on basis of wound closure (p-0.089).

Overall good outcome was observed in 96.9% cases of insulin group as compared to 75% cases of control group. Poor outcome was reported in 25% cases of control group as compared to 3.1% cases of insulin group (p<0.05) as depicted in Table 3.

Table 2. Comparison of study groups as per change in wound depth

Wound Depth	Group	Mean	SD	SE	p-value
Before Debridement	Insulin	2.25	1.26	0.25	0.77
	Control	2.20	1.08	0.23	
After Debridement	Insulin	2.71	1.12	0.25	0.85
	Control	2.77	1.18	0.26	
Week 1	Insulin	2.19	0.09	0.22	<0.05
	Control	2.27	1.14	0.20	
Week 2	Insulin	1.72	0.85	0.20	<0.05
	Control	1.92	1.02	0.19	
Week 3	Insulin	1.31	0.82	0.17	<0.05
	Control	1.59	0.80	0.19	

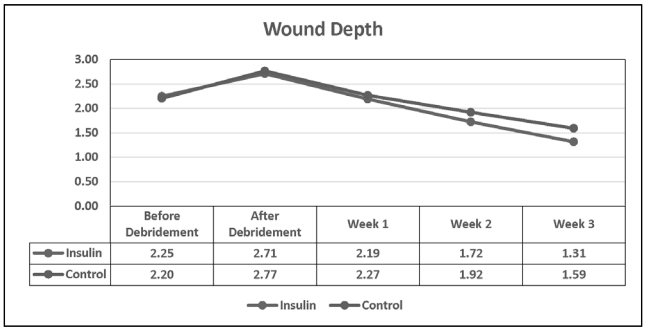

Figure 2. Wound depth change over time.

Table 3. Comparison of study groups as per final outcome

Outcome	Group		Total
	Control	Insulin	
Good	24	31	55
	75.0%	96.9%	85.9%
Poor	8	1	8
	25%	3.1%	12.5%
Total	32	32	64
	100.0%	100.0%	100.0%
p-value < 0.05			

5. Discussion

Diabetic Foot Ulcers (DFUs) by their delayed healing nature as well as complication lead to morbidity and thus pave way for mortality. By increasing mean hospital stay the patient is further burdened economically as well as socially and thus lowering the quality of life. Several new methods of wound care were designed among which local insulin therapy is gaining popularity. Topical Insulin therapy is a novel method in the healing of DFUs by stimulating the growth and development of different cell types and affects proliferation, migration, and secretion by keratinocytes, endothelial cells, and fibroblasts[11-13]. But the results of various trials comparing it with conventional wound dressing had equivocal results. Hence, we planned to study the efficacy of local application of insulin in promoting faster healing of Diabetic Foot ulcers.

A total of 64 patients presenting with diabetic foot ulcers were included and randomly divided into one of the following two groups (32 each) using computer generated random numbers: Complete general & local examination was done. Local wound site was fully examined taking into considerations the extent as well as situation of the ulcer. Comparison in ulcer size and characteristics at the time of admission and discharge or intervention was performed to determine the efficacy of intervention. The final outcome was classified into two subcategories i.e. Good or Poor outcome at the time of discharge.

6. Demography

Mean age of study subjects in present study was 53.6 and 53.1 years in control and insulin group respectively. Male Preponderance was observed in both groups (87.5% in Control and 90.6% in insulin group respectively).

This is similar to the findings of National health department survey (N.H.D.S) survey at USA where highest incidence of DFUs being in age group of 45 to 64 years[5]. The incidence being higher age group can be

well explained by fact that diabetic foot is a disease due to complication of diabetes mellitus. Complications of diabetes increase with age. Also, diabetes is disease of mostly elderly.

Male Preponderance was also observed in review of literature by Rieber *et al.*[14]. In a study by Lone *et al.*[15] women constituted only one third of the cases of DFUs. India being a male dominated country and lack of medical care given to females may also be a contributing factor as incidence of diabetes is almost similar in males and females.

7. Effects on Wound Healing

Banting discovered Insulin in the year of 1921 and its many benefits in regulating blood glucose levels have been documented. The use of insulin for non-diabetic purposes was popular in the early part of the 20th century but took a backseat during the 1940s and 1950s, and interest in its use became reinvigorated during the latter half of the century[15]. Daily injections of insulin were used to accelerate fractured bone healing in rats, incision wounds of the skin, healing in the distal limb of horses, and in cutaneous ulcerations in diabetic and non-diabetic mice[16,17]. Insulin was also used in the 1960s to treat diabetic wounds in humans, and more recently, insulin spray preparations have been successfully used to treat patients with diabetic ulcers. Furthermore, this hormone has been used to treat burns in humans as well as animal models and has striking evidence of favourable outcome with the strong proof that insulin stimulates healing, thereby decreasing the time of wound closure. However, the underlying mechanisms of insulin-induced improved healing are far from being understood and are yet being investigated[18].

Insulin has long been recognized as an important contributor to wound healing, and many studies have demonstrated the positive effects of insulin on wound healing. IGF, which has a high sequence of similarity to the hormone insulin, has been shown through in vivo studies to stimulate the proliferation, migration and extracellular matrix excretion by keratinocytes, endothelial cells, fibroblasts and even promote the reformation of granulation tissue. Topical formulations of insulin were utilized in the 20th century in an attempt to control local hyperglycaemia of peripheral tissue. However, later investigations have focused on topical insulin applications as it relates to IGF.

The amino acid chain in the IGF is similar to pro-Insulin, which is manufactured in the pancreatic Langerhans cells, with 86 amino acids (Insulin is produced when a 35-amino acid chain - C-peptide - detaches from proinsulin-25). IGF-1 binds to at least two cell surface receptors: The IGF-1 Receptor (IGFR) and the insulin receptor. The IGF-1 receptor seems to be the "physiologic" receptor, binding to IGF-1 at significantly higher affinity than it binds the Insulin receptor heterodimers. Binding studies show that IGF-1 binds the insulin receptor 100-fold well than insulin, which does not correlate with the actual potency of IGF-1 in vivo at inducing phosphorylation of the insulin receptor and hypoglycemia[19,20].

In present study, appearance of granulation tissue and decrease in wound depth was significantly faster in insulin group as compared to control group. Overall good outcome was observed in 96.9% cases of insulin group as compared to 75% cases of control group ($p<0.05$).

In the study by Goenka *et al.*[21], the healing rate in the insulin treatment group was higher than in the control group, regardless of wound size. In studies done by Pierre *et al.*[19] in 1998, healing time was reduced from 6.5 ± 1.0 days with placebo to 4.7 ± 1.2 days during insulin infusion ($P < 0.05$).

Reddy *et al.*[22] studied the efficacy of topical use of insulin in terms of (1) rate of wound healing (2) hospital stay. Improvement of the wound in the form of diameter and depth was seen with increased proliferation of granulation tissue in the insulin group.

Swaminathan *et al.*[23] in a similar study, randomized 32 patients each in two groups, i.e. with insulin dressings (Group A) and Group B with regular saline dressings. The average depth of ulcer in insulin group was 8.7 mm before treatment and 8.2 mm in saline group. There was statistically significant difference ($p<0.05$) in the improvement of ulcer depth-wise in the insulin group before and after treatment. The average size of the ulcer was 4.1 cm^2 in insulin group and it was 3.9 cm^2 in saline group ($p<0.01$).

In other studies, done by Greenway *et al.*[10] and Kanth *et al.*[24], wound healing rates were significantly accelerated in insulin groups and were comparable to our study.

Thus, to summarize, insulin dressing decreases time required for healing. Our study has the limitation of having a very small sample size, but our study has indeed

highlighted the effectiveness of insulin role in wound healing and further encouraged the research on this topic.

8. Conclusion

Comparison in ulcer size and characteristics at the time of admission and discharge or intervention was performed to determine the efficacy of intervention. The final outcome was classified into two subcategories i.e., Good or Poor outcome at the time of discharge. Following observations were made during the study:

1. Mean age of study subjects was 53.6 and 53.1 years in control and insulin group respectively. The difference was statistically non-significant (p-1.0),
2. Male Preponderance was observed in both groups (87.5% in Control and 90.6% in insulin group respectively). The difference was statistically non-significant (p-1.0),
3. Most of the ulcers belonged to grade 3 according to wagner's grading in control and insulin group respectively (46.9% *vs* 43.8%). While 37.5% and 28.1% were in grade 4 no significant difference was observed on basis of grade of wound (p-0.79),
4. In about 78.1% of patients of insulin group, granulation tissue appeared by first week as compared to 53.1% in control group. By week 2 and 3, 90.6% and 96.9% cases in insulin group developed granulation tissue as compared to 68.8% and 75% in control group respectively. The difference was statistically significant ($p<0.05$ for all weeks),
5. No difference was observed in two groups with respect to wound depth after debridement (p-0.85). However, the depth of wound was significantly less in insulin group at week 1,2 and 3 as compared to control group. The percentage decrease in wound depth was more in insulin group than control group by the end of 3rd week (51.66% *vs* 42.6%; $p<0.05$),
6. No difference was observed in two groups with respect to wound surface area after debridement (p-0.51). However, the surface area of wound was significantly less in insulin group at week 1, 2 and 3 as compared to control group. The percentage decrease in wound depth was more in insulin group than control group by the end of 3rd week (36% Vs 28.26%; $p<0.05$),
7. Primary closure was observed in 62.5% and 84.4% patients while STSG was required in 37.5% and 15.6% cases of control and insulin group respectively. No significant difference was observed in conventional and VAC group on basis of wound closure (p-0.089),
8. None of the cases in any group required amputation of leg, and
9. Overall good outcome was observed in 96.9% cases of insulin group as compared to 75% cases of control group. Poor outcome was reported in 25% cases of control group as compato 3.1% cases of insulin group ($p<0.05$).

Topical insulin therapy appears to be superior compared to conventional dressings in the treatment of diabetic foot ulcers in terms of early appearance of granulation tissue and decrease in wound depth. Our results thus confirm that topically applied insulin can accelerate wound healing in chronic ulcer without any systemic side effects. We thus conclude that use of topical insulin is safe and effective in patients with diabetic foot ulcers.

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