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COMPARISON OF TOPICAL INSULIN DRESSING WITH CONVENTIONAL DRESSING IN HEALING OF DIABETIC FOOT ULCERS

General Surgery

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ABSTRACT

The Diabetic ulcer is a major complication in patients with diabetes and is a major cause of morbidity and increased hospital admissions leading to prolonged hospital stay. Diabetic Patients have up to a 25% risk of developing a diabetic foot ulcers. Diabetic foot ulcer is one of the commonest sequelae following trauma or infection mainly around the distal ends of limbs where the vascularity is relatively decreased due to effects of diabetes. Important step in managing diabetic ulcer is offloading the wound by using appropriate therapeutic footwear1,2 daily saline or similar dressings to provide a moist wound environment,debridement when necessary, antibiotic therapy if cellulitis is present3,4 optimal control of blood glucose, evaluation and correction of peripheral vascular insufficiency.

Insulin stimulates the growth and development of keratinocytes, endothelial cells and fibroblasts and help proliferation, and tissue healing.5 Hence the present study was undertaken to compare the effect of topical insulin and conventional dressing in healing of diabetic foot ulcers.

The objective of the present study was to compare the effect of topical insulin with conventional dressing in healing of diabetic foot ulcers.

Objectives: To compare the efficacy of topical insulin dressing with conventional dressing in healing of diabetic foot ulcers, in terms of ;

- No. of days required for healing
- Rate of granulation tissue formation
- Quality of graft bed and skin graft up take
- effect on bacterial load
- Side effects of topical insulin dressing

Results: Our results indicate the presence of subtle insulin responsiveness in diabetic skin tissue, regardless of the presence of impaired insulin sensitivity, which could be the cellular and molecular mechanism of insulin accelerating diabetic wound healing.

Conclusion: The use of topical Insulin strongly suggests accelerated wound healing in diabetic foot ulcers. Topical insulin in chronic ulcer is safe and effective without any systemic side effect. Topical insulin signifi cantly reduces the hospital stay of patients with diabetic foot ulcers. Early return to work decreased economical load.

KEYWORDS

diabetic foot ulcers , rate of wound healing, topical application of insulin

INTRODUCTION

In this millennium where mankind has succeeded in deciphering the human genetic code, wound management still remains an enigmatic challenge. The history of wound healing is as old as the history of mankind.[6] Chronic wounds, especially non-healing types, are one of the most common surgical conditions that a surgeon comes across. From time immemorial, doctors have been trying many methods to treat such wounds.[7]

The effect of insulin on wound healing has been confirmed in various animal and wound models, including cutaneous ulcerations, incision wounds and fracture wounds [8]. The effectiveness of insulin on wound healing has also been observed in donor sites of burn patients[9]. Our previous studies found that insulin accelerates nondiabetic wound healing by stimulating the migration of keratinocytes and vascular endothelial cells, thus improving re-epithelialization and angiogenesis. Insulin regulating wound inflammation response is also responsible for insulin-induced wound healing [10-12]. Insulin receptor substrate (IRS) proteins serve as important signaling molecules for insulin, and insulin induced association of IRS-1 and PI-3 kinase have been found to be involved in insulin regulated growth-promoting effects in skin[13].

The wound healing process consists of sequential and overlapping phases, in which dysfunction of any stage could lead to improper wound healing [14]. Diabetes mellitus is one of the major diseases that causes pathological changes and leads to impaired wound healing. Twenty-five percent of diabetic patients will have a diabetic foot ulcer in his or her lifetime[15]. It has been widely accepted that diabetic impaired healing is not a singular etiology [16,17]. Disturbance of glucose metabolism, dysregulation of inflammatory response, insufficient of growth factors secretion, and dysfunction of repairing cells and cell signaling are all involved in the morbidity of diabetic impaired wound healing [18-20].

Wound healing is a complex biological process influenced by several agents such as insulin-like growth factor (IGF) and human acidic fibroblast growth factor (rh-aFGF). In vivo studies have shown that IGF can stimulate the proliferation and differentiation of endothelial cells and fi broblasts and thus, promote granulation tissue regeneration contributing to wound healing.

AIM

The aim of this study was to evaluate the efficacy of topical insulin in healing of diabetic foot ulcers.

MATERIALS AND METHODS

A prospective study has been conducted at Department of surgery , Adichunchungiri institute of medical sciences, mandya, India, between September 2019 and April 2020 comprising of 50 cases.

Patients with Grade I and II foot ulcers according to Meggit – wagner classification and Patients on oral hypoglycemic agents or insulin for diabetes management were included in the study whereas patients with Grade III, IV, V foot ulcers according to Meggit – wagner classification, Age less than 18 years, Ulcer of size more than 5*5 cm,Immunocompromised state like HIV, patients with varicose veins ad decreased vascularity of lower limb, chronic ulcer of other etiology were excluded from the study.

A detailed clinical examination was carried out. Patients fulfilling the inclusion criteria were randomized prospectively into two groups, Group A and Group B.

Group A received insulin dressing and Group B received normal saline dressing without insulin. All diabetic patients were brought under glycemic control with appropriate antidiabetic therapy. Before enrolling the patients for study, culture and sensitivity swab of all the ulcers was taken and ulcers were cleaned with normal saline. Surgical debridement of dirty wounds was done under anesthesia. Then the ulcers were included in the study. Time required for preparing the ulcers from the time of admission till enrollment in the study was considered as wound preparation time. While considering the hospital stay of patients this wound preparation time was not taken into account.

In Group A, ulcers were cleaned with normal saline and then irrigated with 4 units (0.1 ml) of human soluble insulin (Actrapid) in 1 ml

normal saline (0.9%) for each 10 cm2 of wound. The solution prepared was sprayed on the ulcer surface with an insulin syringe twice daily and ulcer was left to dry and then covered with sterile cotton gauzes.

In Group B, ulcers were cleaned with normal saline without insulin and covered with sterile gauzes.

All patients were treated empirically with Cap. Ampicillin 250 mg, Cloxacillin 250 mg qid at the time of admission. Later antibiotics had been changed according to pus culture and sensitivity reports.

Wounds were measured using a sterile transparent paper placed on the wound to mark the wound borders. The two largest perpendicular diameters were measured using a ruler (in millimeters). To calculate the wound area, these two diameters were multiplied to obtain area of ulcer in mm2.

Even though topical Insulin is not absorbed systemically, to evaluate the safety, random blood glucose levels (BSL) (R) were measured with a glucometer 10 minutes before and 1 hour after application of topical insulin in Group A patients.

Ulcer size was measured once a week till 12 weeks or till the complete healing of ulcer, whichever was earlier.

The end point of the study has been taken as complete wound epithelisation or healing of wound at the end of 12 weeks or whichever was earlier. Rate of wound healing was calculated as the difference between the primary wound on the day 1, till complete wound healing and is reported in terms of mm2 / week as a marker of healing.

STATISTICAL ANALYSIS

Results from all patients who enrolled in the study were tabulated and expressed as mean and standard deviation. Statistical evaluation of the data was performed using the SPSS version 11. Comparisons between groups were performed using the "Z value test" and "chi-square test". All results were considered to be signifi cant at the 5% critical level (P < 0.05).

RESULTS

All 50 patients achieved wound closure. The incidence of diabetic patients was 60% in Group A and 72% in Group B which was statically non-significant and comparable.

ETIOLOGY	GROUP A-insulin dressing	GROUP B-normal saline dressing
Diabetes	25	25

Distribution of cases of in study groups In our study, the mean ulcer size on day 1 was 670 ± 215 mm2 in Group A and 629 ± 257 mm2 in Group B which was comparable and statistically not significant.

Table 3: Comparison of ulcer size in mm2 on Day 1 in study groups

Ulcer size on day 1 (mm2)	GROUP A	GROUP B	t value	P value
	670+/-215	629+/-257	0.49	>0.05 (NS)

No. of days required for healing was 38 ± 17.03 days in Group A and 44.3 ± 17.5 days in Group B which were comparable and statistically significant [Table 4].

Table 4: Comparison of no. of days required for healing in study groups.

No of days required for healing	GROUP A Mean+/-SD	GROUP B Mean+/-SD	Z value	P value
	38+/-17.3	44.3+/-17.5	1.02	<0.05(S)

The mean rate of healing was 130 ± 25.3 mm2 /wk in Group A and 95.1 ± 34.9 mm2 / wk in Group B which were comparable and statically significant [Table 5].

Table 5: Comparison of rate of healing in study groups.

Rate of healing (mm2 /wk)	GROUP A Mean+/-SD	GROUP B Mean +/-SD	t value	P value
	130.2+/-25.3	95.1+/-34.9	3.30	<0.005(HS)

The mean hospital stay was 40.1 ± 16.6 days in Group A and 46.2 ± 17.9 days in Group B which were comparable and statically significant [Table 6].

Table 6: Comparison of hospital stay in study groups

Hospital stay	GROUP A Mean+/-SD	GROUP B Mean+/-SD	Z value	P value
	40.1+/-16.6	46.2+/-17.9	0.99	>0.05S

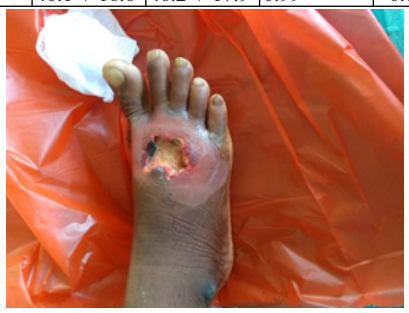


Fig no 1- day 1

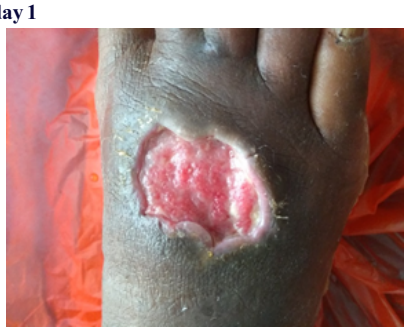
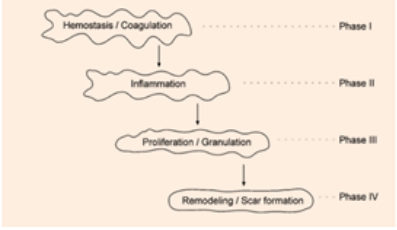


Fig no 2- day 11

DISCUSSION

Since Banting's discovery of Insulin in 1921, many benefits beyond blood glucose regulation have been documented. The use of insulin for non-diabetic purposes was popular in the early part of the 20th century , was "forgotten" during the 1940s and 1950s, and it became again reinvigorated during the latter half of the century.[21] For example, daily injections of insulin were used to improve 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 .[22,23] Insulin was also used in the 1960s to treat diabetic wounds in humans , and more recently, insulin spray has been successfully used to treat patients with diabetic ulcers. Furthermore, this hormone has been used to treat burns in humans , rats , and rabbits with good success. With the strong evidence that insulin stimulates healing, thereby decreasing the time of wound closure, the underlying mechanisms of insulin-induced improved healing are far from being understood.[24] Our study had demonstrated positive effects of insulin on wound healing.

Insulin is a peptide hormone with multiple physiological roles. It regulates blood glucose levels and is known to have a beneficial role in wound healing. Since insulin can potentially help restore the integrity of damaged skin, it is of interest in the field of wound repair, particularly owing to its low cost relative to other growth factors, and, thus, is more likely to be considered for incorporation into wound dressings, bio adhesive films and hydrogels [25].



Research consistently highlights the importance of the insulin receptor, a transmembrane molecule, activated by insulin, IGF-I and IGF-II.It belongs to a large class of tyrosine kinase receptors found in all cell types, including keratinocytes and fibroblasts [26]. Liu, et al. [27] showed that topical application of insulin to excision wounds stimulates keratinocyte migration.

The dermatological properties of insulin have been studied for almost a century [28]. Rosenthal demonstrated that topically applied insulin

increases wound tensile strength and decreases healing times in Wistar rats [29]. Similarly, Udupa and Chansouria applied a linear musculoperitoneal wound in rats and administration of 2 units of insulin per 100 g subcutaneously led to faster wound healing in insulin-treated rats when compared to a control group. Histological analysis of wound tissue showed an earlier appearance of collagen fibres with more dense and well-oriented morphology versus control animals [30]. Recently, Zhang et al. [31] tested local insulin-zinc injections on skin donor sites of rabbits. Subcutaneous injections of 0.25 units of long acting insulin-zinc suspensions were directly administered to the backs of dermatomed adult rabbits. Insulin was injected every other day and compared to controls consisting of placebo and zinc suspension alone. With localised injection, wound healing was accomplished in 9 days, significantly faster than any of the control groups and without signs of major systemic side effects.

Lima et al. [32] investigated the effect of a topical cream, containing insulin, showing that it accelerated wound healing and induced a rescue in the levels of tissue proteins involved in the early steps of insulin action, as mentioned above [32].

In this and other studies, an initial wound area correlated with wound healing rate — i.e. larger wounds healed at a faster pace than smaller wounds. However, in the current study, the healing rate in the treatment group was higher than in the control group, regardless of initial wound size.

In our study, number of days required for healing was 38 ± 17.03 days in Group A and 44.3 ± 17.5 days in Group B. Both these Groups A and B had diabetic patients. But the ulcers in Group A required less number of days than Group B which were comparable and statistically significant . In studies done by Pierre et al.,[15] in 1998, healing time was reduced from 6.5 ± 1.0 days with placebo to 4.7 ± 1.2 days during insulin infusion ($P < 0.05$) and study by Rezvani et al. in 2009[8] found a healing time of 41.85 ± 20.56 days in the insulin group and 43.50 ± 22.85 days in the normal saline dressing group. In other studies done by Greenway et al.,[33] Kanth et al.,[34] Rezvani et al.,[32] wound healing rates were signifi cantly accelerated in insulin groups and were comparable to our study. Omid et al. found the rate of healing to be 40.09 mm2 /day in the insulin group and 32.24 mm2 /day in the normal saline dressing group. Thus, 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.

CONCLUSIONS

The use of topical insulin strongly suggests accelerated wound healing in diabetic foot ulcer, found to be safe and effective without any systemic side effect. In our study it shows reduced hospital stay of the patients.

REFERENCES:

1) Beuker BJ, van Deursen RW, Price P, Manning EA, van Baal JG,Harding KG. Plantar pressure in off-loading devices used indiabetic ulcer treatment. Wound Repair Regen. 2005;13:537-42
2) Hilton JR, Williams DT, Beuker B, Miller DR, Harding KG. Wounddressings in diabetic foot disease. ClinInfect Dis. 2004;39:S100-3.
3) Edmonds M, Foster A. The use of antibiotics in the diabetic foot. Am JSurg. 2004;187:25S-28S
4) O'Meara SM, Cullum NA, Majid M, Sheldon TA. Systematic review ofantimicrobial agents used for chronic wounds. Br J Surg. 2001;88:4- 21.
5) Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.Systematic reviews of wound care management:(2). Dressings andtopical agents used in the healing of chronic wounds. Health TechnolAssess. 1999;3:l-35.
6) Barb ul Adrian. Brunicardi FC, Wound Healing. In: Schwartz's Principles of Surgery. 9th ed, Ch.9, New York, McGRAW-HILL; 2005: 209-33.
7) Cooper L, Johnson C, Burslem F, Martin P. Wound healing and infl ammation genes revealed by array analysis of 'macrophage less' PU.1 null mice. Genome Biology 2004;6:R5.
8) Joseph B. Insulin in the treatment of non-diabetic bed sores. Ann Surg. 1930;92:318–319.
9) Rosenthal SP. Acceleration of primary wound healing by insulin. Arch Surg. 1968;96:53–55.
10) Liu Y, Petreaca M, Yao M, Martins-Green M. Cell and molecular mechanisms of keratinocyte function stimulated by insulin during wound healing. BMC Cell Biol. 2009;10:1.
11) Liu Y, Petreaca M, Martins-Green M. Cell and molecular mechanisms of insulin-induced angiogenesis. J Cell Mol Med. 2009;13:4492–4504.
12) Chen X, Liu Y, Zhang X. Topical insulin application improves healing by regulating the wound inflammatory response. Wound Repair Regen. 2012;20:425–434.
13) Takahashi Y, Akanuma Y, Yazaki Y, Kadowaki T. Formation of distinct signalling complexes involving phosphatidylinositol 3-kinase activity with stimulation of epidermal growth factor or insulin-like growth factor-I in human skin fibroblasts. J Cell Physiol. 1999;178:69–75.
14) Robson MC, Steed DL, Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. Curr Probl Surg. 2001;38:72–140.
15) Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005;293:217–228.
16) Jeffcoate WJ, Harding KG. Diabetic foot ulcers. Lancet. 2003;361:1545–1551.
17) Ehrlichman RJ, Seckel BR, Bryan DJ, Moschella CJ. Common complications of wound healing. Prevention and management. Surg Clin North Am. 1991;71:1323–1351.
18) Ferguson MW, Herrick SE, Spencer MJ, Shaw JE, Boulton AJ, Sloan P. The histology of diabetic foot ulcers. Diabet Med. 1996;13(Suppl 1):S30–33.
19) Spravchikov N, Sizyakov G, Gartsbein M, Accili D, Tennenbaum T, Wertheimer E. Glucose effects on skin keratinocytes: implications for diabetes skin complications. Diabetes. 2001;50:1627–1635.
20) Blakytny R, Jude E. The molecular biology of chronic wounds and delayed healing in diabetes. Diabet Med. 2006;23:594–608.
21) Lawrence RT, Salter JM, Best CH. The effect of insulin on nitrogen retention in the hypophysectomized rat. Br Med J 1954;2:437-9.
22) Hardman JG, Limbird LE, Gilman AG, editors. The pharmacological basis of therapeutics. 10th ed. New York, NY; McGraw-Hill; 2001. p.1679-81.
23) Panuncialman J, Hammerman S, Carson P, Falanga V. Wound edge biopsy sites in chronic wounds heal rapidly and do not result in delayed overall healing of the wound. J Wound Repair Regan 2010;18:21-5.
24) Liu Y, Petreaca M, Yao M, Martins-Green M. Cell and molecular mechanisms of keratinocyte function stimulated by insulin during wound healing. BMC Cell Biol 2009;10:1.
25) Hrynyk M, Neufeld RJ (2014) Insulin and wound healing. Burns 40(8): 1433-1446.
26) Pelegrinelli FF, Thirone AC, Gasparetti AL, Araujo EP, Velloso LA, et al. (2001) Early steps of insulin action in the skin of intact rats. J Invest Dermatol 117(4): 971-976.
27) Liu Y, Petreaca M, Yao M, Martins-Green M (2009) Cell and molecular mechanisms of keratinocyte function stimulated by insulin during wound healing. BMC Cell Biol 10(1): 1-15.
28) Joseph B (1930) Insulin in the Treatment of Non-Diabetic Bed Sores. Ann Surg 92(2): 318-319.
29) Rosenthal SP (1968) Acceleration of primary wound healing by insulin. Arch Surg 96(1): 53-55.
30) Udupa KN, Chansouria JP (1971) The role of protamine zinc insulin in accelerating wound healing in the rat. Br J Surg 58 (9): 673-675.
31) Zhang X J,Wu X, Wolf SE, Hawkins HK, Chinkes DL, et al. (2007) Local Insulin-Zinc Injection Accelerates Skin Donor Site Wound Healing. J Surg Res 142(1): 90-96.
32) Lima MH, Caricilli AM, de Abreu LL, Araújo EP, Pelegrinelli FF, et al. (2012) Topical insulin accelerates wound healing in diabetes by enhancing the AKT and ERK pathways: A double-blind placebocontrolled clinical trial. PLoS One 7(5): e36974.
33) Greenway SE, Filler LE, Greenway FL. Topical insulin in wound healing: A randomised, double-blind, placebo-controlled trial. J Wound Care 1999;8:526-8.
34) Kanth S, Bhat PR. Wound Dressing – Topical Insulin. J SWCR 2011;4:11-4.