

A Prospective Study to Evaluate the Role of Topical Insulin in Healing of Chronic Ulcer

Arpit Agrawal¹, Chandra Shekhar Amb², Virendra Pratap Singh Saytode³,
Virendra Pachole⁴

¹Senior Resident, Department of General Surgery, Nandkumar Singh Chauhan
Government Medical College, Khandwa, Madhya Pradesh

²Assistant Professor, Department of General Surgery, Nandkumar Singh Chauhan
Government Medical College, Khandwa, Madhya Pradesh

³MS General Surgery, Senior Resident, Department of General Surgery, NSCB Medical
College, Jabalpur, Madhya Pradesh

⁴Senior Resident, Department of General Surgery, Nandkumar Singh Chauhan
Government Medical College, Khandwa, Madhya Pradesh

Received: 08-04-2022 / Revised: 22-04-2022 / Accepted: 29-04-2022

Corresponding author: Dr. Virendra Pachole

Conflict of interest: Nil

Abstract

Background: Healing of chronic wounds (CW) is one of the most complex processes in the human body. Insulin-like growth factor-I role has been demonstrated in animal studies. However, human studies are disproportionately fewer.

Aims and Objectives: To evaluate the efficacy of local insulin therapy by comparing insulin dressings with regular saline dressings.

Materials and methods: Seventy patients admitted with CW in Index Medical College, Hospital and Research Centre, Indore, Madhya Pradesh, were studied prospectively. Patients were randomized into Group A and Group B. Each group was subdivided into A1, A2, A3, B1, B2, and B3. Patients with diabetes were grouped as A1 and B1, infective ulcers in groups A2 and B2, and traumatic ulcers in groups A3 and B3. 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 in the study. Ulcer size was measured once a week for 8 weeks. The study's endpoint has been taken as complete wound epithelialization or healing of wound up to 8 weeks. The rate of wound healing was calculated as the difference between the primary wound on day one till complete wound healing and is reported in terms of mm²/week as a marker of healing.

Results: The mean age in group A was 44.486 years and in the control group was 48.8 years. The rate of wound healing in insulin dressing (Group A) was better than in saline dressing (Group B). Hospital stay was less in the insulin dressing (Group A) than in the saline dressing (Group B). The healing rate in the treatment group was higher than in the control group, regardless of initial wound size. There were no episodes of hypoglycemia due to topical insulin. The mean number of days required for healing was 38.7 days in Group A1 and 47.67 days in Group B1 (p = 0.001). The number of days required for healing was 37.87 days in Group A2 and 46.11 days in Group B2 (p=0.005). The number of days required for healing was 37 days in group A3 and 45.5 days in group B3. It was comparable and significant. The difference in the

hospital stay of the two groups was studied using an independent sample T-test was found to be significant ($p < 0.05$).

Conclusion: Topical insulin dressing in chronic non-healing ulcers is more effective in the early healing of ulcers than normal saline dressings. There is a significant decrease in the mean area of the ulcer.

Keywords: Healing Rate, Diabetes Mellitus, Insulin Therapy, Ulcer Healing, Ulcer Size.

This is an Open Access article that uses a fund-ing model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Chronic wounds (CW) are characterized by a wound that has failed to heal in an orderly process that results in satisfactory anatomic and functional integrity or an adequate anatomic and functional result. Most wounds that have not healed in 3 months are considered chronic[1].

Globally, approximately 6 million people suffer from CW. Indian prevalence of CW is 4.5 per 1000 population compared to acute wounds (10.5 per 1000 population)[2,3].

Several substances, including insulin-like growth factors (IGF) and growth factors from human acidic fibroblasts, play a role in wound healing. Endothelial and fibroblast growth and differentiation can be stimulated by IGF, which has been demonstrated to contribute to wound healing in vivo investigations[4].

Insulin is a growth factor that was proved to stimulate angiogenesis, collagen formation, matrix formation, and granulation tissue proliferation in several preclinical studies[5,6]. A present randomized study was carried out to know the efficacy of local insulin therapy by comparing insulin dressings with regular saline dressings.

Materials and Methods

The present prospective study was performed on 70 patients admitted with CW in Index Medical College, Hospital and Research Centre, Indore, Madhya Pradesh.

Cases were studied according to the definite plan outlined in special performa, which includes a detailed history of presenting illness, personal history, family history, the record of general examination, investigation, treatment, and follow-up of patients.

Patients with chronic ulcers such as infective ulcers, postoperative surgical wounds, diabetic ulcers, and wound size less than 50 cm² were included. In contrast, patients with more than 70 years of age, immunodeficiency, pregnancy, osteomyelitis, varicose ulcer, burns, and multiple organ dysfunction syndromes were excluded.

A detailed clinical examination was carried out. Patients fulfilling the inclusion criteria were randomized into Group A and Group B groups. Each group was subdivided into subgroups 1 and 2, i.e., subgroups A1, A2, A3, and subgroups B1, B2, and B3. Patients with diabetes were grouped as A1 and B1, infective ulcers in groups A2 and B2, and traumatic ulcers in groups A3 and B3.

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 in the study. The 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;

this wound preparation time was not considered during the hospital stay.

In Group A, ulcers were cleaned and rinsed with 4 units (0.1ml) of human soluble insulin (actrapid) in 1ml normal saline (0.9ml) for every 10 cm² of the wound. The solution prepared was sprayed on the ulcer surface with an insulin syringe once daily, and the 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.

Wounds were measured using a sterile method using a ruler with the two largest perpendicular diameters of the wound. Two diameters were multiplied to calculate the wound area to obtain the area of ulcers in mm².

Random blood sugar was measured 10 minutes before and 30 min later after applying insulin over the wound in group A patients.

Ulcer size was measured once a week for 8 weeks. The study's endpoint has been taken as complete wound epithelialization or healing of wound up to 8 weeks. The rate of wound healing was calculated as the difference between the primary wound on day one till complete wound healing and is reported in terms of mm²/week as a marker of healing.

Procedure Planned

The wound was prepared by debridement under anaesthesia by removing all the dead tissue debris slough leaving behind healthy granulation tissue. Patients' investigations were sent like complete blood count and random blood sugar and pus culture and sensitivity, antibiotics were started as per sensitivity report. The wound was cleaned daily with normal saline, and then the cases and controls, as selected randomly, were dealt with as follows.

In Group A, ulcers were cleaned with normal saline and then rinsed with 4 units (0.1 ml) of

human soluble insulin (Actrapid) in 1 ml of normal saline (0.9%) for every 10 cm² of wounds. The solution prepared was sprayed on the ulcer surface with an insulin syringe once daily, and the 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. Wounds were measured using 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 the area of the ulcer in mm². Even though topical insulin is not absorbed systemically, to evaluate the safety, random blood glucose levels (BSL) ® 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 8 weeks or till the complete healing of the ulcer, whichever was earlier.

The study's endpoint has been taken as complete wound epithelialization or healing of wounds up to 8 weeks. The rate of wound healing was calculated as the difference between the primary wound on day 1 till complete wound healing and is reported in terms of mm²/ week as a marker of healing.

Statistical analysis

Statistical analysis was done using Microsoft EXCEL software and the SPSS computer program. Chronic non-healing ulcers in the study group had a better wound healing rate in mm²/wk. Quantitative data were expressed as mean and standard deviation, whereas categorical data were expressed as numbers and percentages. The difference in the rate of healing of the two groups was studied using an independent sample T-test. A p-value of <0.05 was considered significant.

Results

The age of the patients ranged from 15 to 70 years. The maximum number of cases belong to the age group of 40 to 55 years. The mean age in group A was 44.486 years and in the control group was 48.8 years.

In both the study and control groups, diabetes was more common among males than females. Traumatic ulcers are also more common in males; 67% of the patients were male, and 33% were female. Among both groups, gender distribution was comparable.

Table 1: Comparison of rate of healing in study groups

Rate of healing (mm ² /week)	Group A	Group B	P-value
Diabetic	144.87±34.16	111.30±44.90	0.013
Infective	163.83±44.94	120.56±35.32	0.04
Traumatic	165.1±64.82	111.71±25.65	0.05

Data are expressed as Mean ± SD

The rate of granulation tissue formation was assessed up to 8 weeks to heal ulcers. The rate of wound healing in insulin dressing (Group

A) was better than in saline dressing (Group B).

Average Healing Rate(mm²/wk)

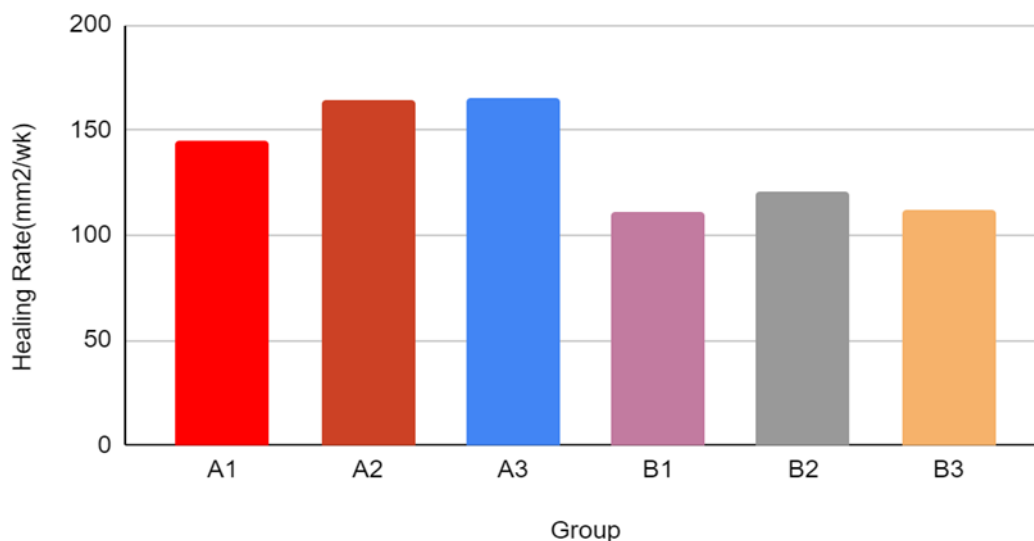


Figure 1: Comparison of rate of healing in subgroups.

Table 2: Comparison of hospital stay in study groups(in days)

Hospital stay	Group A	Group B	P-value
	Mean	Mean	
Diabetic	38.7	47.67	0.001
Infective	37.87	46.11	0.005
Traumatic	37	45.5	0.042

Our study found that the hospital stay was less in the insulin dressing (Group A) than in the saline dressing (Group B).

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

Ulcer size on day 1 (mm ²)	Group A	Group B	P-value
	Mean	Mean	
Diabetic	2046.95	2342.78	0.27
Infective	2366.75	2576.89	0.615
Traumatic	1707.14	2055.13	0.302

In the current study, the healing rate in the treatment group was higher than in the control group, regardless of initial wound size.

In the insulin dressing group patients, the random blood sugar before and after the dressing was determined, and there were no episodes of hypoglycemia due to topical insulin.

Table 4: Comparison of BSL (Random) before and after dressing in Group A

Parameter	Before dressing (n=35)	After dressing (n=35)	Z Value	P-Value
	Mean ± SD	Mean ± SD		
BSL (R) (mg/dl)	120±11.306	114±9.439	2.492	0.013

In our study, the mean number of days required for healing was 38.7 days in Group A1 and 47.67 days in Group B1 ($p = 0.001$). The number of days required for healing was 37.87 days in Group A2 and 46.11 days in Group B2 ($p=0.005$).

The number of days required for healing was 37 days in group A3 and 45.5 days in group B3. It was comparable and significant. The difference in the hospital stay of the two groups was studied using an independent sample T-test was found to be significant ($p<0.04$).

Discussion

Since Banting discovered insulin in 1921, many benefits beyond blood glucose regulation have been documented. Insulin for non-diabetic purposes was widespread in the early part of the 20th century. It was

"forgotten" during the 1940s and 1950s. It became again reinvigorated during the latter half of the century. For example, daily insulin injections were used to improve bone healing in rats, incision wounds of the skin, healing in the distal limb of horses, and cutaneous ulcerations in diabetic and non-diabetic mice. 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 successfully treated burns in humans, rats, and rabbits. With the strong evidence that insulin stimulates healing, thereby decreasing the wound closure time, the underlying mechanisms of insulin-induced improved healing are far from being understood. Our study demonstrated the positive effects of insulin on wound healing.

**Figure 1: Images showing infective ulcer healing with use of topical insulin**

Our study calculated the rate of healing of ulcers by determining the area healed in mm² divided by the time in weeks. The rate of wound healing in group A is better than in group B.

In our study, the rate of wound healing was better in the insulin dressing group. The patients with diabetes mellitus responded better than the normal saline dressing group. The rate of wound healing compared in diabetic patients with insulin dressing and saline dressing. The rate of wound healing compared in infective ulcer patients with insulin dressing and saline dressing. The rate of wound healing compared in traumatic ulcer patients with insulin dressing and saline dressing.

In our study, the number of days required for healing was 38.70 days in Group A1 and 47.67 days in Group B1. Both these Groups A1 and B1 had diabetic patients. But the ulcers in Group A1 required fewer days than in Group B1, and the difference was statistically significant ($p=0.001$). The number of days needed for healing was 37.87 days in Group A2 and 46.11 days in Group B2, comparable and statistically significant ($p=0.005$). The days required for wound healing were 37 days in group A3 and 45.5 days in group B3, comparable and statistically significant ($p=0.04$).

In studies, an initial wound area correlated with wound healing rate — i.e., larger wounds healed faster 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. The initial wound size did not correlate with the rate of wound healing or hospital stay in the insulin dressing group or the non-insulin dressing group.

In the insulin dressing group patients, the random blood sugar before and after the dressing was determined (Group A1, A2, and A3), and there was no significant decrease in

the blood sugar levels. There were no episodes of hypoglycemia or any other complications due to applying the topical insulin. Topical insulin was safe when used over chronic ulcers with proper dilution.

In studies done by Pierre et al. in 1998, the healing time was reduced from 6.5 ± 1.0 days with placebo to 4.7 ± 1.2 days during insulin infusion ($P < 0.05$)[7]. The study by Rezvani et al. 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[8]. In Greenway et al.[9], Kanth et al.[10], Rezvani et al.[8], wound healing rates were significantly accelerated in insulin groups and were comparable to our study.

Omid et al. found the healing rate to be 40.09 mm²/day in the insulin group and 32.24 mm²/day in the normal saline dressing group. In a study conducted by Swaminathan et al., the mean ulcer area in the insulin group was 4.1 cm². In the saline group, it was 3.1cm² on day 1. The reduction in mean ulcer size was 2.5 cm² in the insulin group and 1.0cm² in the saline group after 4 weeks[11].

In another study conducted by Pandey et al., the mean ulcer area at the time of admission in the insulin group was 4.8 ± 0.6 cm², 5.35 ± 0.6 cm² in the normal saline group. Also, the mean difference in ulcer surface area after the 12th day was 3.2 ± 0.7 cm² in the insulin group and 2.9 ± 0.8 cm² in normal saline[12].

Another study conducted by Prasad et al. had 13 cm² as the mean ulcer size in the insulin group and 14.51 cm² in the control group. At the end of 20 days, the insulin group's mean reduction in the ulcer area was 4.06 cm². In contrast, the control group was 3.5 cm² which was statistically significant[13]. In the study by Goenka et al., topical insulin strongly suggests accelerated wound healing in chronic ulcers, found to be safe and effective without any systemic side effects.¹⁴ Our study shows reduced hospital stay of the patients.

Our study and the various studies mentioned above establish the safe and effective use of topical insulin as a dressing for chronic non-healing ulcers.

Thus, we have concluded that topical use of insulin in chronic non-healing ulcers decreases the time required for healing, and it has helped reduce the patients' hospital stay. Our study has the limitation of having a minimal sample size. Still, our study has indeed highlighted the effectiveness of insulin's role in wound healing and further encouraged research on this topic.

Conclusion

In our study to evaluate the efficacy of topical insulin dressing in chronic non-healing ulcers, we conclude that it is effective in the early healing of ulcers compared to normal saline dressings. There is a statistically significant decrease in the mean area of the ulcer.

Topical insulin application could bring down the chronicity of dressing in the patients. It did not have any systemic complications. It is cost-effective. With adequate hemoglobin, albumin, and controlled glycemic index in diabetic patients with appropriate antibiotics, topical insulin seems to be a fair alternative to other pharmacological applicants, costing much for the patient.

The topical dressing is not a single-handed approach to healing ulcers; it is a multidisciplinary team approach that includes good sugar control in diabetic patients, wound care, dressings, timely surgical interventions & most of all, patient motivation & education regarding the ulcer care.

References

1. Frykberg RG, Banks J. Challenges in the Treatment of Chronic Wounds. *Adv Wound Care* (New Rochelle). 2015;4(9):560-582.
2. Liu Y, Petreaca M and Martins-Green M. Cell and molecular mechanisms of insulin-induced angiogenesis. *J Cell Mol Med* 2009; 13: 4492-4504.
3. Chen X, Liu Y, and Zhang X. Topical insulin application improves healing by regulating the wound inflammatory response. *Wound Repair Regen* 2012; 20: 425-434.
4. Garoufalia Z, Papadopetraki A, Karatza E, Vardakostas D, Philippou A, Kouraklis G, Mantas D. Insulin-like growth factor-I and wound healing, a potential answer to non-healing wounds: A systematic review of the literature and future perspectives. *Biomed Rep.* 2021 Aug;15(2):66.
5. Robson MC, Steed DL, and Franz MG. Wound healing: biologic features and approaches to maximize healing trajectories. *Curr Probl Surg* 2001; 38: 72-140.
6. Singh N, Armstrong DG and Lipsky BA. Zhang XJ, Chinkes DL, Sadagopa Ramanujam VM, Wolfe RR. Local injection of insulin-zinc stimulates DNA synthesis in skin donor site wound. *J Wound Repair Regen* 2007; 15:258-26.
7. Pierre EJ, Barrow RE, Hawkins HK, Nguyen TT, Sakurai Y, Desai M, et al. Effect of insulin on wound healing. *J Trauma* 1998; 44:342-5.
8. Rezvani O, Shabbak E, Aslani A, Bidar R, Jafari M, Safarnezhad S. A Randomized double-blind, placebo- controlled trial to determine effects of topical insulin on wound healing. *Ostomy Wound Manage* 2009; 55:22-8.
9. 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.
10. Kanth S, Bhat PR. Wound Dressing – Topical Insulin. *J SWCR* 2011; 4:11-4.
11. Swaminathan R. Effectiveness of topical insulin in management of chronic diabetic foot ulcers. *Indian Journal of Basic and Applied Medical Research.* 2014; 3(3):455-9.

12. Pandey S et al. Efficacy of Topical Insulin Dressings V/S Normal Saline Dressing On Diabetic Foot Ulcer - A Hospital Based Study, Subharti Medical College, Meerut. IOSR Journal of Dental and Medical Sciences 2018; 17(01):47-50.
13. Prasad A et al. To Study The Efficacy of Topical Insulin Vs. Conventional Dressing on Wound Healing In Diabetic Foot Ulcers, Department of General Surgery SRM Medical College, Hospital and Research Centre, Kattankulathur, TN, India. IOSR Journal of Dental and Medical Sciences 2018; 17(4):33-38.
14. Goenka G, Athavale VS, Nirhale DS, Deshpande N, Agrawal K, Calcuttawala M. Role of topical use of insulin in healing chronic ulcers. Med J DY Patil Univ 2014; 7:579-83.