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Effect of Insulin on Healing of Pressure Sore

Farzaneh Ebrahimifard [1]; Navid Nooraei [2,*]; Mohammad Fathi [2]; Mina Dehghani [2]

[1]Department of General Surgery, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
[2]Department of Anesthesia, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

*Corresponding author: Navid Nooraei, Department of Anesthesia, Modarres Hospital, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-9123366106, E-mail: navidnooraei@gmail.com

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Background: Pressure ulcers are skin lesions at bony prominences that develop due to direct pressure on soft tissue. They occur more frequently in paraplegic patients and elderly who are taken care at nursing homes. Nevertheless, patients who underwent major surgeries such as heart and lung operation with prolonged operation and postoperation period are also susceptible to develop soars. These ulcers lead to increased hospitalization rate and high healthcare costs. Because insulin exerts some of its effects through insulin-like growth factor, insulin would be effective on wound healing process.

Objectives: Our aim is to evaluate the effect of topical insulin on healing of pressure sores.

Patients and Methods: This double-blinded clinical trial was conducted on patients with pressure ulcer in Shahid Modarres Hospital, Tehran, Patients were randomly allocated to two groups. One of these groups was treated with normal saline and the other group by insulin solution (1 U/mL) and after 14 days, wounds were evaluated for size reduction (mm^2) and presence of granulation tissue.

Results: A total of 44 patients, with female to male ratio of 1:1 and mean age of 61.84 (12.63) years, participated in the study; 20 patients (45.5%) had hemoglobin level of < 12 mg/dL and 22 patient (50%) had diabetes (Fasting blood glucose > 6.99 mmol/L). Mean size of sore before and after intervention was respectively 532.27 (390.3) mm^2 and 397 (362.5) mm^2 with significant reduction in size. However, the changes in sore size before and after intervention between two groups showed no significant difference. In addition, the difference was not significant between patients with and without diabetes. Anemia did not have any effect on wound healing.

Conclusions: Although reduction in wound size was slightly better with insulin dressing than with normal saline (10% vs. 8.5% of sore surface, respectively) this difference was not statistically significant. There was significant decrease in wound size and presence of granulation tissue after 14 days in all cases irrespective of used dressing.

Keywords: Pressure Ulcer; Insulin Solution; Granulation Tissue; Wound Healing

1. Background

Pressure wounds are caused by direct pressure on soft tissue. They usually develop on bony prominences after long bed rest. since a large area of skin is baring the weight and at the same time contacting the bed surface, the pressure on blood vessels causes dysfunction and insufficiency in blood supply of the area results in necrosis of the tissue (1-6). Mortality, sepsis, and osteomyelitis rate increase following pressure ulcers (4-6).

Several treatment modalities have been shown to be effective including adequate cleansing and debridement, using pressure reducing surfaces, convenient dressing, optimal nutrient therapy, electrical stimulation, radiant heat, biological therapies like growth factors, negative pressure therapy, using antibiotics to decrease infection, and surgery (3, 4, 6-9).

Different studies have shown the beneficial effect of dressing on pressure ulcer; the most common dressings are wet saline gauze, transparent films, hydrocolloids, alginates, foams, hydrogel, hydrofibers, polymer films, absorbing granules, and silver-impregnated dressings (3, 4, 6-8, 10). Nonetheless, developing new treatment modalities is of great importance. Nowadays using topical agents for treating wounds has attracts attention. There is lack of evidence for the benefits of many topical products that are currently used (11).

With regard to topical agents, the effectiveness of topical zinc on wound healing has been demonstrated in several studies (12-15). Moreover, several studies have suggested the effectiveness of different growth factors on wound healing in humans and rats (5, 9, 16-21). However, little is known about topical insulin and its effect on wound healing.

Wound healing involves complex mechanisms that results in cell adhesion, migration, proliferation, differentiation, and apoptosis (22-24). Lately, it has been indicated that insulin receptors are present in all cells such as fibroblasts and keratinocytes and it can also activate phosphatidylinositol-3 kinase and mitogen-activated protein kinase signals in skin fibroblasts and keratinocytes (25). Therefore, insulin can stimulate cell development and proliferation, migration, and secretion by fibroblasts and keratinocytes (22, 26-29), which indicate that topical

insulin can play a role in wound healing if insulin level could be maintained at a convenient level (25).

Topical insulin improved burn ulcers in rats through reducing inflammation and increasing epithelialization (26). Moreover, it had an effect on healing cutaneous ulcerations in diabetic and non-diabetic rats (30), Injection of insulin-zinc solution at the ulcer site accelerated wound healing in rabbits (25). Systemic insulin injection was used to treat burn wounds in human (31) and a study showed the effectiveness of topical insulin on wound healing in human (32).

Previous studies mostly represented the effect of insulin on wound healing in animals. Although there is evidence on beneficial effects of insulin on wound healing, no application method has been demonstrated to be appropriate for the routine clinical use.

2. Objectives

In this experimental double-blinded clinical trial, we aimed to evaluate the effect of topical insulin on healing of pressure wounds in patients with bedsores.

3. Patients and Methods

3.1. Study Design

We performed an experimental double-blinded clinical trial on 44 patients with bed sore in Shahid Modarres , Tehran, Iran, in order to evaluate the effect of topical insulin on healing process of pressure sores.

3.2. Subjects and Setting

All patients with bedsore in Shahid Modarres Hospital were identified by reading nursing notes and asking nurses. Then a general surgeon examined the patients and after the diagnosis was made, patients signed a written consent.

Subjects were included if they had pressure ulcer of grade 2 or 3. Patients with a history of cancer, hypersensitivity to insulin, known disease such as pneumonia, immunodeficiency, and antibiotic consumption were excluded. Sample size was calculated based on statistical formula and reviewing other studies (n = 44). From 50 patients, six were excluded of whom for did not have the inclusion criteria and two refused to participate.

Subjects were randomly allocated to two groups of case and control, based on their code number. Patients with odd and even code numbers were assigned to case and control groups, respectively. In the case group, topical insulin and normal saline were used in dressing the wounds in the case and control groups, respectively, three times a day.

For dressing the wound in the case group, gauze was soaked in insulin (made of 10 mL of crystal insulin in 1000 mL of normal saline) was used. Each gauze was contained approximately 10 mL of the solution. The number of used gauzes corresponded to the wound size in a way the whole wound was covered with a layer. The study was double-blinded as the pharmacy staff contributed with coding the drug vials and drugs were used for patients individually according to their code. Neither the patients nor the staff were aware of the kind of used dressing. The staff members, who did the dressings, were two nurses in different shifts who were responsible for wound dressing with a same taught and coordinated procedure.

The study was continued for two weeks in both groups. Wound size, wound secretion, and granulation tissue were evaluated initially and after 14 days. A general surgeon evaluated the lesions. The measurement techniques and instrument (transparency paper and direct observation) were also the same.

3.3. Measurements and Statistical Analysis

The wounds were observed closely and their depth, width, and length were measured. Instruments used in this measurement and dressing included pencil, paper, sterile transparent paper, marker, gauze, cotton, normal saline, insulin syringe, surgical tape, bandage, and crystal insulin. In both case and control group, usual laboratory and physical examinations were performed and patients with suspected conditions were excluded. In both groups, fasting blood sugar (FBS), blood sugar at 4 P.M. (BS4pm), and glycosylated hemoglobin (HBA_{1C}) was measured in order to assess the effect of insulin on blood glucose and to compare its effect on wound healing in patients with and without diabetes. After insulin was administered, blood glucose was measured two times in the first day and one time in the second day, which revealed no hypoglycemia. If a single patient had several wounds, only one of them would be studied.

3.4. Statistics

Matching of patients considering age and sex was done previously. Statistical analysis was performed using SPSS 12 (SPSS Inc., Chicago, IL, USA), and significance level was set at $P < 0.05$. In both groups, the wounds size before and after treatment and the difference between them had normal distribution; hence, paired-samples t test was used to analyze the data. Considering the limited number of samples and the distribution range that was not normal, Levene's test was used to compare variances.

Distribution of anemia was normal in each group; however, the disparity distribution was normal so the Mann-Whitney U test was used. The independent-samples t test was used to compare the groups with respect to diabetes status.

4. Results

The study participants were 44 patients including 22 males and 22 females. The mean age of patients was 61.84 ± 12.63 years (range, 22-78). Insulin was used for dressing the wound in 23 patients (52.3%).

Before treatment, the mean wound size was 532.27 ± 390.30 mm^2. The largest and smallest wound size was respectively 2208 and 80 mm^2 (Table 1). According to the surgeons, granulation tissue did not develop in wounds of two patients (4.5%); however, granulation tissue was formed in 95.5% of the wounds. In addition, hemoglobin level was < 12 mg/dL in 20 patients (45.5%) and > 12 mg/dL in the rest (54.5%). Half of the patients had diabetes (FBS > 126) (Table 1). In both groups, the wound size and their difference before and after intervention had normal distribution; therefore, paired-samples t test was used to analyze the data. The mean wound size after intervention was 397 ± 36.5 mm^2. After intervention, the sizes of the largest and smallest wounds were respectively 1995 and 69 mm^2. The difference between wound size before and after intervention irrespective of the type of dressing was statistically significant (P < 0.001).

The changes in wound size after treatment showed no significant deference between the study groups. The power of the study was 13% (Table 2).

Considering the limited number of samples and the distribution of variables, which was not normal, Levene's test was used to compare variances.

Table 1. Basic Characteristics of Patients and Pressure Sores [a, b]

Parameter	Value
Age, y	61.84 ± 12.63 [c]
Sex	
Female	22 (50)
Male	22 (50)
HB	
≥ 12 mg/dL	24 (54.5)
< 12 mg/dL	20 (45.5)
FBS	
≥ 7 mmol/L	22 (50)
< 7 mmol/L	22 (50)
Sore size, mm^2	
Before treatment	532.27 ± 390.30 [c]
After treatment	397 ± 362.5 [c]
Treatment method	
Insulin	23 (52.3)
Normal saline	21 (47.7)

[a] Abbreviations: FBS, fasting blood sugar; and HB, hemoglobin.
[b] Data are presented as mean ± SD or No. (%).
[c] P < 0.05, t test as appropriate.

Table 2. Wound Size Decrease After Treatment [a]

Treatment Group	Wound Size Decrease
Topical Insulin	48.13 ± 42.76 [b]
Normal Saline	39.14 ± 27.43 [b]

[a] Data are presented as mean ± SD.
[b] P < 0.05, t test as appropriate

Regarding anemia, distribution of wound size before and after intervention was normal in each group; however, the disparity distribution was not normal. Therefore Mann Whitney U test was used and showed no differences between wound size two groups. Regarding diabetes, the independent-samples t test was used and the difference was not significant between the groups.

Patients with diabetes were divided in two groups of case and control and were compared in the means of wound size reduction and the difference was insignificant. However, according to the limited number of samples in both groups, the results were inconclusive. In this multivariate study, after analyzing the wound size, there was a significant correlation between wound size before and after intervention (r = 0.998, P < 0.001). In addition, there was inverse correlation between wound size before intervention and decrease in wound size (r = 0.78, P < 0.001) (Table 2).

To compare the results more accurately, the decrease in wound size was reported as ratio of wound size reduction. Furthermore, the ratio of wound size reduction was 8.7% in patients with the usual dressing and 10% in patients with insulin dressing (P > 0.05).

5. Discussion

Pressure sores are morbidities in all healthcare centers. Incident rates have been shown to be 0.4% to 38% in hospitals, 2.2% to 23.9% for long-term care, and 0% to 17% for home care (13 and 3 of it) (3, 33). It is calculated that nearly 1.3 to 3 million adults are suffering from pressure sores with an estimated 500 to 40000 dollars expends for treating each ulcer (3, 34). Therefore, developing new methods for treatment as well as prevention is beneficial to the healthcare systems.

We conducted a study on human pressure sores and found that the ratio of wound size reduction was 8.7% in topical insulin group and 10% in control group, which demonstrated no significant difference between the two groups. Our results are inconsistent with most of the studies on animals. In Greenway et al. study, selective standard wounds were created on rats and effects of three solutions, namely, insulin, normal saline, and zinc, were studied. Wounds were histopathologically examined ten days after injury and revealed that among the three solutions, normal saline had the least and zinc had the greatest effect on healing (32).

In another study, burn wounds were created on back of young rats and were subdivided in two groups. Subcutaneous insulin was administered to a group of rats for three days. Skin sections were analyzed later by means of histochemistry and quantitative polarization microscopy. The results showed that insulin had accelerated wound healing, which was associated with reduced inflammation and increased collagen in the skin tissue (26).

In a study concerning insulin-zinc solution effect on wound healing, partial thickness skin donor ulcers were created on the back of adult rabbits. Then wound heal-

ing days were compared after local intradermal injection of either insulin-zinc or zinc alone. The mean number of days for complete healing was used as an indicator of wound healing. In the insulin group, wounds were healed after 11.2 ± 2.3 days in comparison with 15.1 ± 4.1 days for complete healing in the control group (25).

Two other studies also evaluated insulin effect on wound healing in diabetic and non-diabetic animals. In the first study, four groups of rats (non-diabetic rats treated with topical insulin, non-diabetic rats receiving topical distilled water, diabetic rats treated with topical insulin, and diabetic rats receiving topical distilled water) were examined. Wound healing was evaluated by means of wound contraction rate, complete epithelialization time, and histologic findings. The results revealed that topical insulin enhanced wound healing, which was evident by shortening complete epithelialization time, rate of wound closure, and thicker epidermis in insulin-treated diabetic and non-diabetic rats (35). A similar study was done on infected cutaneous ulcerations in mice the showed that topical insulin established increased rates of wound healing in comparison with the control group in both diabetic and non-diabetic mice (30).

In contrary to these studies, our study was conducted on human samples and we examined bedsores, which is a kind of pressure sore rather than standard created ulcers and burn wounds. Moreover, we used insulin topically without zinc. Our wound healing indicator was clinical including direct observation and measuring wound size rather than histopathologic examination and results were compared in terms of wound size decrease by rate and raw amounts, which showed no difference between patients with and without diabetes.

In a another study by Greenway et al. conducted on 11 human candidates (five with and six without diabetes), two uniform cuts was created on each individuals forearms, one wound was treated with insulin-zinc solution and the other with normal saline, without using dressings. They found that in both diabetic and non-diabetic groups, healing were accelerated (for 2.4 ± 0.8 days); It was unclear whether it was due to the effect of insulin, zinc, or both (32).

In our study, patients' wounds were not uniform; they were of different size and were not formed intentionally. Moreover, pressure was an important factor in their development. The used insulin solution had no zinc and all wounds were dressed. Our case and control patients were completely different considering demographics and confounding factors.

The significant outcome in Greenway et al. study might be due to confined number of participants (n = 11) and omitting confounding factors. In contrast, complete matching of variables was impossible in our study and although the study was done on 44 samples, the results were insignificant.

In the only research with comparable results to ours, insulin with hyperosmotic glucose solution was used externally for treating pressure sore and the results were compared with moist burn ointment in terms of average healing time. The results demonstrated that in the trial group, average healing time was 11.6 ± 2.7 days for grade 2 pressure sores and 12.9 ± 3.4 days in the control group, which showed no statistically significant difference between them. However, the average healing time for grade 3 pressure sore in the trial group more significantly decreased than that of the control group did (22.3 ± 4.3 vs. 24.8 ± 3.9 days) (36). In our study, although topical insulin was used for treatment of grade 2 or 3 pressure sores without using hyperosmotic glucose, our results were consistent with the mentioned study in means of insulin effect on grade 2 pressure wounds.

5.1. Limitations of Study

In this study, the sample size was small, which might be due to using preventive methods including advanced nursing training in the intensive care unit for patient care, changing patients position and washing them frequently, and using fluctuating mattress commonly, which resulted in decreased number of patients with pressure sore in our center.

Tissue granulation was not formed in only two cases (4.5%); however, this variable could have been omitted using different eligibility criteria. In other patients without considering dressing type or confounding variables, granulation tissue was formed after 14 days of treatment and significant decrease in wound size was seen; however, because removing factors causing pressure wound and modifying confounding factors such as anemia and malnourishment can be effective in the wound healing process, the results were not conclusive.

Finally, although there was no significant difference in wound size between two groups, considering the low power of the study and the difference in the raw results of wound size reduction, the results could have been different if the sample size was larger. In explanation of correlation between wound size prior to the intervention and decrease in wound size, we found that the larger the wound was at the beginning, the lower the decrease rate would be. Moreover, wound size reduction rate was more accurate with higher statistical power in defining correlations and comparing data. It is recommended to use this variable in further studies.

In conclusion, our study demonstrated that topical insulin does not decrease wound size in comparison to routine usage of normal saline. However, as long as the study has some limitations, the results might be inconclusive. It is suggested to do the same research on human bedsore with a larger number of samples and to use “wound size decrease ratio” to obtain more accurate results.

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