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Comparison of the Effect of Topical Crystalline Insulin and Oxygen on Bedsore Healing in ICU Patients, A Single Blind Clinical Trial

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Abstract

Background: *Pressure ulcer is an important diagnosis and care need of patients admitted to intensive care units, which in addition to delaying recovery, imposes high costs on the patient and the treatment system. The effectiveness of topical oxygen and insulin has been confirmed in various studies, but so far the two methods have not been compared. The aim of this study was to compare the effect of crystalline insulin and topical oxygen on pressure ulcer healing.*

Methods: *In this single-blind clinical trial, 60 patients with grade 3 bed sores hospitalized in the intensive care unit of Kashani Hospital in Shahrekord were allocated in 3 groups including the first group (routine treatment and topical regular insulin 100), the second group (routine treatment and local oxygen) and the third group (routine treatments wound washing and camphil dressing) twice daily for two weeks using block randomization method. At previous times, 1 and 2 weeks after the intervention, the condition of the wound was assessed by the Pressure Ulcer Scale for Healing (PUSH) criteria (wound size, wound secretion and tissue type). Data were analyzed by SPSS software.*

Results: *Before the intervention, the mean wound area, wound secretion, wound degree and PUSH score were not significantly different in the 3 groups. At 1 and 2 weeks after the intervention, the mean wound area, wound secretion, wound grade and PUSH score in the two groups of insulin and local oxygen were not significantly different from each other (P-value>0.05), but compared with the control group was significantly lower (P-value<0.0001).*

Conclusion: *The use of insulin and topical oxygen caused a significant improvement in bed sores compared to routine treatment and their effects were similar and both are recommended to accelerate bed sores healing in hospitalized patients.*

Keywords: Pressure ulcer, Crystal insulin, Topical oxygen.
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Introduction

Bedsore or pressure ulcer is one of the major problems of patients hospitalized in medical centers[1]. Pressure ulcers increase the length of hospital stay and cause a delay in the patient's recovery. It also increases the risk of infection and mortality[2, 3]. Additionally, its occurrence affects the person socially, psychologically, and physically, so it decreases the quality of life[4]. The prevalence of pressure ulcers is estimated at 10-20%. The annual cost of its treatment is high and includes nursing care, wavy mattress, skincare, nutritional support, and expensive dressings[3, 5]. Treatment methods used in the management of pressure ulcers include assessing the ulcer severity, relieving pressure, reducing frictional forces, changing position, nutritional support, removing necrotic tissue, controlling infection, maintaining ulcer moisture, and dressing[6]. One of the common dressings used in the treatment of pressure ulcers is hydrocolloid dressing, the most significant of which are comfeel, duoderm, and hydrocoll[7].

A high recovery rate has been reported for the above dressings[8]. They are associated with disadvantages such as high costs, allergies, and severe reactions[7]. Thus, researchers are looking for alternative or complementary drugs to reduce side effects and accelerate the healing process[9]. A low level of oxygen is one of the characteristics of chronic ulcers. It has been observed that oxygen treatment can accelerate ulcer healing[10, 11]. Insulin is also used in ulcer healing. Its beneficial role in ulcer healing has been proven[12]. Different studies have measured the effectiveness of topical oxygen[10, 11] and insulin[12, 13]. However, two methods have not been compared so far.

The present study aims to evaluate and compare the effects of topical crystal insulin and topical oxygen in the healing of pressure ulcers in hospitalized patients.

Materials and Methods

Study design: The present was conducted as a single-blind clinical trial on patients hospitalized in the intensive care units of Shahrekord Kashani Hospital and suffering from pressure ulcers in 2020.

The inclusion criteria included patients aged 19-65 years with severe concussion (GCS<8) and a Stage 3 (Grade 3) pressure ulcer, no organ failure, no diabetes, burns, chronic skin disease, diarrhea, vascular problems and hypoalbuminemia, no history of smoking, drug use or alcohol addiction, lack of infectious symptoms in the ulcer (swelling, redness around the ulcer, and bad-smelling and purulent secretions), lack of cachexia symptoms (folding in the back of the arm, the appearance of the patient, the prominence of the zygomatic arch, and emptying of the temporal cavity), not using systemic corticosteroids during the past year, and

completion of the consent form by the patient or the patient's legal guardian. The exclusion criteria included organ failure, hypoxic patients, and patient death during the study. Also, the urine urea balance test was used to monitor the nutrition of the patients. If the patient's urea balance was negative, the caloric level was calculated and the problem was solved by nutrition counseling.

Based on Azimian et al.'s study (2008), since the difference between the intervention and control groups after the intervention was 16.6, the minimum sample size according to the formula 1-2 was estimated at 14 people in each group considering the standard deviation of 0.15, the first and second type errors of 0.5 0 and 0.2, respectively. Given the possibility of a dropout rate of 30%, 20 patients were placed in each of the 3 groups[14]. In this study, an initial 60 participants were selected via convenience sampling. Subsequently, the participants were allocated into three study groups using permuted block randomization (block size of 6). The randomization sequence was generated using Random Allocation software. To minimize bias in the outcome assessment, the statistical analyst was blinded to the group allocations (i.e., intervention types) throughout the data analysis phase. At baseline, the three groups were comparable, and the number of hospitalization days was matched across all groups. Insulin or topical oxygen was used in the intervention groups, in addition to routine treatments, which include daily washing of the ulcer with normal saline and then covering the ulcer with a common dressing (comfeel). Regular insulin 100 (Eli Lilly's Iletin II Pork Insulin) was used topically twice a day for two weeks in the topical insulin group in addition to routine care. Accordingly, for every 10 cm^2 of the ulcer, 4 units of regular insulin were dissolved in 1 cc of normal saline serum and applied to the ulcer using an insulin syringe, and then covered with a sterile gauze pad[15]. In addition to daily routine care twice for two weeks, oxygen was used with a flow of 10 liters per minute for 20 minutes through a sterile cover that covers the entire ulcer in the topical oxygen treatment group (oxygen interface was connected to an oxygen manometer containing distilled water from one side and to a sterile urine bag on the other side). The area around the urine bag was opened and covered the surface of the ulcer. One side was without an adhesive bandage for gas exchange[16]. For the third group (control group), the ulcer site was washed with normal saline and then routine care, which included covering the ulcer with a common dressing (comfeel) for two weeks, was used.

The ulcers of the patients in both groups were fully examined by an experienced person and the ulcer condition was recorded based on Pressure Ulcer Scale for Healing (PUSH) criteria before the intervention and at the end of the first and second weeks after the intervention. In this scale, three factors including the ulcer size, the amount of exudate, and the tissue type are used to determine the ulcer condition. The highest score in the push system is 17 and the lowest score is 3. Ulcer area was measured in square centimeters (cm^2) using a graduated and sterile spatula. The amount of exudate was assessed using the ordinal criteria of the PUSH tool (Scores 1-3), as detailed below. The amount of ulcer secretions was examined with the following criteria:

Score 1: The amount of secretions is small (the gauze does not get wet at all)

Score 2: The amount of secretions is moderate (one piece of gauze gets wet)

Score 3: Secretions in a large amount (two pieces of gauze get wet)

Also, tissue healing was examined using the following criteria:

Grade 1: The skin is fully closed.

Grade 2: The skin color is pink and there is no secretion at all.

Grade 3: The skin is pale and has some secretion.

Grade 4: The skin is black and has secretions for a whole day.

The primary outcome was defined as the change in the total PUSH score from baseline to the end of the first and second weeks. This composite score served as the main indicator of overall wound healing. Secondary outcomes included the individual changes in each PUSH subcomponent (ulcer area, exudate amount, and tissue type score) analyzed separately.

A single wound specialist, who was experienced in pressure ulcer care, performed all PUSH assessments to ensure consistency. The wound status was evaluated at baseline (before the intervention) and subsequently at the end of the first- and second-weeks post-intervention.

Statistical analysis: Data were analyzed in SPSS24 software. Chi-square tests and independent T-test were used for demographic variables and analysis of variance or covariance (between groups) followed by the Tukey post hoc test and repeated measurement analysis (within groups) was used to compare variables of ulcer area, amount of secretions, tissue type, and push score. In this research, the intention-to-treat approach was applied and the significance level of the tests was considered at P-value<0.05.

Results

In this clinical trial, 60 patients with grade 3 bedsores were treated in three groups, including the routine care group, regular insulin 100 plus routine care group, and topical oxygen plus routine care group (20 in each group). Among the 60 patients studied, 34 (56%) were male, and the mean age of the patients was 42.2±12.5 years. There was no significant difference between the 3 groups regarding gender (P-value=0.93) and age (P-value=0.98) (Table 1).

Table 1. Frequency distribution of gender and mean age in the studied groups

Group / Gender	Insulin group N=20 (%) n	Topical oxygen N=20 (%) n	Control group N=20 (%) n	P-value
Male	(55) 11	(55) 11	(60) 12	0.93
Female	(45) 9	(45) 9	(40) 8	
Age (year) Mean±SD	42.2±13.4	41.8±13.3	42.6±11.4	0.98

Before the study, there was no significant difference between the three studied groups regarding the ulcer area (P-value=0.99). Also, there was no significant difference between the two insulin and topical oxygen groups regarding the ulcer area at the end of the first and second weeks (P-value>0.05). However, a significant difference was observed between the mentioned groups and the control group in this regard (P-value=0.028 and P-value=0.008). There was no significant difference between the three studied groups regarding the amount of ulcer secretion before the study (P-value=0.95).

The amount of ulcer secretion between the two groups of insulin and topical oxygen was not significantly different at the end of the first and second weeks (P-value>0.05). However, a significant difference was found between the mentioned groups and the control group in this regard (P-value<0.001). Before the study, the ulcer was grade 3 in all 3 groups. The ulcer grade was not significantly different between the insulin and topical oxygen groups at the end of the first and second weeks (P-value>0.05). However, a significant difference was observed between them and the control group (P-value<0.001, Table 2).

Table 2. Comparison of mean ulcer area, ulcer discharge, and ulcer grade in the studied groups

Variable	Group / Week	Insulin group N=20 Mean±SD	Topical oxygen N=20 Mean±SD	Control group N=20 Mean±SD	Between-group P-value
Ulcer area	Before intervention	8.05±2.29	8.09±2.29	8.11±2.79	0.99
	The first week	5.85±2.18	5.72±1.99	6.79±2.66	0.028
	The second week	4.03±1.85	3.58±1.65	5.71±2.75	0.008
	Within-group P-value*	<0.001	<0.001	<0.001	-
Ulcer secretion	Before intervention	2.45±0.50	2.45±0.67	2.35±0.49	0.95
	The first week	1.3±0.47	1.1±0.31	1.85±0.37	<0.001
	The second week	0.6±0.51	0.55±0.51	1.3±0.47	<0.001
	Within-group P-value*	<0.001	<0.001	<0.001	-
Ulcer grade	Before intervention	3	3	3	0.001
	The first week	1.05±0.22	1.05±0.22	2	<0.001
	The second week	0.6±0.50	0.6±0.50	1.7±0.47	<0.001
	Within-group P-value*	<0.001	<0.001	<0.001	-

*** Repeated measurement analysis**

Before the study, there was no significant difference between the three studied groups regarding the push score (P-value=0.10). The push score was 8.5±1.1 in the insulin group, 9.05±1.18 in the topical oxygen group, and 9.8±1.4 in the control group at the end of the first week. No significant difference was observed between these groups (P-value>0.05). However, a significant difference was observed between them and the control group (P-value=0.03). At the end of the second week, the push score was 5.55±0.61 in the insulin intervention group, 5.7±1.96 in the topical oxygen group, and 7.8±1.54 in the control group. No significant difference was observed between them (P-value>0.05). However, a significant difference was observed between these two groups and the control group (P-value<0.001, Table 3).

Table 3. Comparison of the mean push scores in the studied groups

Group / Week	Insulin group N=20 Mean±SD	Topical oxygen N=20 Mean±SD	Control group N=20 Mean±SD	Between-group P-value
Before intervention	11.5±1.45	11.0±1.47	12±1.38	0.1
The first week	8.85±1.14	9.05±1.28	9.8±1.4	0.03
The second week	5.55±0.61	5.7±0.66	7.8±1.54	<0.001
Within-group P-value*	<0.001	<0.001	<0.001	-

*** Repeated measurement analysis**

Discussion

The results revealed that the mean ulcer area, ulcer secretion, ulcer grade, and PUSH score before the intervention were not significantly different among the three groups (routine care, regular insulin 100 plus routine care, and topical oxygen plus routine care), indicating comparable baseline ulcer conditions. At 1- and 2-weeks post-intervention, the mean area, secretion, ulcer grade, and PUSH score were not significantly different between the insulin and topical oxygen groups. However, both intervention groups showed significantly greater improvement in all indices compared to the control group, which may suggest the potentially superior efficacy of both topical oxygen and insulin as adjuncts to routine care over routine care alone in healing pressure ulcers.

The present findings on topical oxygen are consistent in direction but show a more modest effect size compared to some prior studies. They align with several experimental and clinical trials reporting the effectiveness of topical oxygen[11, 14, 16]. Azimian et al.'s study indicated that topical oxygen treatment compared to simple dressing reduced ulcer area, secretion levels, and enhanced healing[14]. Similarly, Rezaei et al. suggested that topical oxygen at 10 L/min for 20 minutes accelerates healing and significantly reduces ulcer area, exudate, and promotes granulation tissue formation in ICU patients[16]. However, the reduction in the total PUSH score in our study was less pronounced than that reported by Rezaei et al.[16]. A potential explanation for this discrepancy could be our shorter follow-up period (2 weeks vs. 4 weeks) and our specific patient population with severe brain injury (GCS<8), which may modulate the overall tissue repair response. Other studies support the role of hyperbaric oxygen therapy (HBOT). Enomoto et al. showed that HBOT could lead to complete ulcer healing within one year and appears safe for over 100 sessions in patients with radiation-induced skin ulcers and osteomyelitis, suggesting it as an alternative conservative treatment[11]. Tawfick et al. indicated that oxygen therapy after 12 weeks may heal venous ulcers and reduce recurrence rates and pain[17]. Rao et al. reported in a murine model that topical oxygen treatment for chronic ischemic ulcers accelerated healing, granulation tissue formation, collagen deposition, and angiogenesis compared to controls[18]. Smith et al. also suggested that ten sessions of HBOT could accelerate the ulcer healing process[19]. Thanigaimani et al. reported that topical oxygen might improve the probability of diabetic foot ulcer healing[20], and another study indicated it leads to more healing, reduced ulcer area, and improved quality of life compared to routine care[21]. The crucial role of oxygen in cellular repair processes, including energy production, collagen synthesis, and angiogenesis, underpins these findings[11, 16, 20].

Regarding topical insulin, the efficacy in our study is largely consistent with, though slightly less pronounced than, findings from studies on diabetic ulcers. Various models have suggested the effectiveness of topical insulin in ulcer healing. Lima et al. indicated that topical insulin may significantly accelerate ulcer healing in diabetic patients[22]. Greenway et al. showed that topical insulin, as a growth factor, could possibly accelerate ulcer healing[12]. Attia et al. demonstrated that topical crystalline insulin promoted greater ulcer healing compared to saline without side effects[23]. Stephen et al. found a significantly lower mean ulcer grade in the topical insulin group than in the control group by day seven, with no observed systemic adverse effects such as hypoglycemia or infection[24]. Other studies have also indicated insulin's effectiveness on healing time and rate[25]. The somewhat more modest effect observed in our study could be attributed to the non-diabetic status of our participants. Since insulin's mechanisms are often studied in the context of impaired healing dynamics in diabetes (e.g., correcting relative insulin deficiency or hyperglycemia), its effect in a normoglycemic, severely concussed population might manifest differently.

The proposed mechanisms for both interventions support our results. A constant oxygen supply is vital for cellular homeostasis, energy production, and repair[20]. Topical oxygen is thought to promote healing by stimulating phagocytosis, collagen production, and angiogenesis[11, 16]. Topical insulin appears to improve healing by modulating oxidative and inflammatory responses, increasing macrophage chemotaxis and phagocytosis, promoting keratinocyte migration and re-epithelialization via the PI3K-Akt-Rac1 pathway, improving collagen maturation, and enhancing angiogenesis[13, 26]. Furthermore, topical insulin seems to accelerate healing without causing significant systemic side effects and might be cost-effective[27].

In summary, while both interventions in our study demonstrated clear superiority over routine care alone, their relative efficacy compared to each other was equivalent. The observed effect sizes, though statistically significant, were generally more conservative than those reported in some previous studies focusing on topical oxygen for general pressure ulcers or topical insulin for diabetic ulcers. Key factors potentially contributing to these differences include our study's specific population (non-diabetic, severely brain-injured patients), the relatively short (2-week) intervention and follow-up period, and the single-center design, which may limit generalizability but provides a controlled assessment in a complex clinical cohort.

Conclusion: The results of this study suggest that both topical crystalline insulin and topical oxygen are probably effective adjunctive treatments for accelerating the healing of grade 3 pressure ulcers in ICU patients compared to routine care alone. Their effects appear to be similar over a two-week period. These interventions may offer valuable alternatives in clinical settings. However, further research with larger sample sizes, longer follow-up durations, standardized protocols, and possibly double-blind designs is warranted to confirm these findings, establish optimal treatment parameters, and better understand the long-term comparative effectiveness and cost-efficacy of each modality.

Limitations of the study: Although the findings of this study are promising and directional, further studies with larger sample sizes, longer follow-up periods, double-blind designs, and more diverse populations are needed to definitively confirm the equivalence of insulin and local oxygen efficacy and to establish robust treatment guidelines.

Ethical Considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This study is registered with clinical trial code IRCTID: IRCT20210508051228N2.

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I would like to transparently disclose that we used an artificial intelligence-based writing assistant soley for minor language editing and grammatical editing, clarity and sentence structure in then manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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