Original Article

The Topical Formulation of Whey Protein for the Prevention of Pressure Ulcers in Critically Ill Patients: A Novel Intervention in a Randomized-Controlled Clinical Trial

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Abstract

Background: High prevalence of pressure ulcers (PUs) and their complications are important dilemmas in the intensive care unit (ICU). Therefore this study was designed to evaluate the effectiveness of topical whey protein formulation in preventing PUs in patients admitted to the ICU.

Materials and Methods: In this randomized placebo-controlled clinical trial under registration number [IRCTdeted for blinded article], 80 eligible ICU patients were randomly allocated to receive topical ointment of whey protein or placebo on the sacrum with a diameter of 15 cm twice daily for seven days, in addition to the routine care. The mean risk score for developing PUs was calculated at baseline using the Braden tool, and the PUSH score was used to assess PUs on days 4, 7, and 14. Patients' related demographic and clinical variables were also collected using a medical record for more evaluation.

Results: Our results showed that demographic characteristics and the Braden scores' baseline mean were not significantly different between groups ($P > 0.05$). The repeated measures ANOVA test revealed that the mean scores of PUs at various times were markedly lower in the whey protein than in the placebo group ($P < 0.001$).

Conclusion: This intervention can be routinely added as effective, safe, inexpensive, and accessible care to reduce the incidence of PUs for patients at risk of developing this injury.

Keywords: Intensive care unit, pressure ulcer, whey protein

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Submitted: 10-Sep-2022; **Revised:** 19-Nov-2022; **Accepted:** 26-Dec-2022; **Published:** 30-Jun-2023

Introduction

As one of the most important problems of patients admitted to intensive care units (ICU), pressure ulcers (PUs) could be considered a valuable indicator of the quality of medical services.[1,2] Despite the routine care applied to manage PUs, including decompression, position change, nutritional support, antihypertensive support levels, and advances in technology and awareness, PUs have remained a dilemma for caregivers. ICU patients have a high risk of developing PUs. Excessive use of respiratory equipment, urinary and multiple intravascular catheters, hemodynamic instability, and vasoactive drugs used for hypotension are the most common risk factors for PU in the ICU.[3] In a systematic review study in 2018, Chaboyer *et al*.[4] reported the incidence of PUs in adult ICUs at 10%–25.9% and its prevalence at 16.9%–23.8%.

The high financial burden of PUs is associated with increasing therapeutic costs and the length of hospital stay.[5] In addition

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_302_22

How to cite this article: Samimi S, Abbasi S, Taheri A, Farsaei S. The topical formulation of whey protein for the prevention of pressure ulcers in critically ill patients: A novel intervention in a randomized-controlled clinical trial. Adv Biomed Res 2023;12:168.

to the costs of PU treatment, the risk of its complications and undesirable side effects such as cellulite, endocarditis, sepsis, and death are increasing worldwide. Previous research indicated that each PU increases patients' length of hospital stay in the United States by at least four days and increases the risk of nosocomial infections by 25%, potentially fatal.[6]

Therefore, effective interventions to prevent PUs in ICU patients have priority in the treatment plan and would effectively reduce complications and treatment costs.[7] Various interventions, including different dressings, were evaluated to treat PUs.[8] However, further researches are necessary not only for its management but also to prevent it. One exciting study evaluated the topical milk effects in accelerating wound healing.[7] Milk products have been proven to be a rich source of nutrients beneficial in ulcer healing. According to recently performed studies, modified milk products noted the positive effects in the recovery of wounds in animal studies which could be attributed to the whey protein in milk.[7,9,10]

Topical whey protein exhibited beneficial effects such as increased collagen fibers, increased fibroblasts, and reduced inflammatory cells in the administered area in the animal model, which seems that this product can be potentially valuable for the physical protection of the skin and prevention of PUs.[7] However, there is no background for the topical application of whey protein for PU prevention in animals or humans. Therefore, based on the available evidence, this study was designed to investigate topical whey protein formulation's effect on preventing PUs.

Materials and Methods

This randomized placebo-controlled, double-blinded clinical trial under registration number [IRCTdeleted for blinded article] was performed on 80 ICU patients admitted to two tertiary referral hospitals located in the middle of Iran from October 2019 to January 2021.

Ethical approval was obtained from the ethical committee of the institutional review board [deleted for blinded article].

The study's sample size was calculated as 40 patients in each group based on previous data,[11] considering the significance level of 0.05 and 80% power ($\beta = 0.8$), with p1 = 0.028, p2 = 0.257 for the sample size formula.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 [P_1(1-P_1) + P_2(1-P_2)}{P_1(1-P_2)^2}$$

All adult patients willing to participate in this study within the age group of 18–80 years, without PUs or any skin problem, with the possibility of ICU stay duration above seven days, were recruited conveniently during the first 24 hours of ICU admission. Patients with any condition compromised adequate skin circulation were not included (such as anemia, traumatic bleeding, hemodynamic instability, receiving vasoactive medications, diabetes, advanced heart failure, active cancer, kidney failure, or any vascular problem). Moreover, those patients with local hypersensitivity reactions to our formulation or less than 14 days study period for any reason (change in the care setting, discharge, or death) lost follow-up. They did not enter for clinical outcome analyses.

Randomization and blinding

After obtaining written informed consent, eligible patients were allocated to the placebo or intervention group using the random blocking method. We selected block sizes of two, four, or six with a random list generated by a computer for a 1:1 allocation to study groups. In this study, the patients and the trained Pharm D (who evaluated PU scores) were blind about the whey protein ointment and placebo containers. However, the data were collected based on the number randomly assigned to each patient to ensure a blinded assessment of the outcome.

In addition to the routine care, patients in our study received topical ointment of placebo or whey protein in the sacrum with a diameter of 15 cm twice a day for seven days to prevent PUs. Both ointments were rubbed on the patients' skin (in intervention and control groups) without pressure or massage. The care routinely conducted for these patients included daily evaluation of patients' skin, repositioning at least every four hours, putting small pillows between pressure areas for removal and reduction of pressure, use of moisturizers for dry skin, control of fecal and urinary incontinence, and cleansing of skin in the case of contamination.

Patients' sacrums in both groups were evaluated for PUs on days 4, 7, and 14 according to the PUSH criteria.

The PUSH score is a fast, accurate, and valid tool to measure pressure sore status over time by examining three areas: wound size, exudate amount, and tissue type. The total score is rated from 0 to 17 (0 means healing). In the case of developed PUs, the greatest width (side to side) and length (head to toe) were multiplied to obtain the surface area estimation in square centimeters (cm^2).

We assessed the risk of developing PUs on admission based on the Braden scoring tool for all recruited patients. Braden score is another common, standard questionnaire used worldwide to predict PU risk based on six categories: sensory perception, activity, mobility, moisture, nutrition, friction, and shear. This scoring ranges from 6 to 23 points, with lower scores representing a higher risk for PUs.[12,13] The Braden assessment score could be stratified into four risk groups: mild risk (scores 15–18), moderate risk (13–14), high risk (10–12), and very high (equal to or less than 9).[12,14] We also recorded demographic variables (age, sex), the reason for ICU admission (trauma, surgery, and internal medicine), underlying diseases (hypertension, cardiovascular disease, kidney, and lung disease), and the patient's history of addiction or smoking and daily sequential organ failure assessment (SOFA) score.

Whey protein and placebo topical ointment formulation

For preparing whey protein ointment, 0.5 g of whey protein powder (Karen Company, Iran) was dissolved in 3 ml of

distilled water. The prepared solution was added to 15 g of eucerin (Shahtalebi Laboratory, Iran) as the base of ointment and mixed to obtain a uniform 2% (w/w) whey protein-containing ointment.

The placebo ointment only consisted of eucerin (Shahtalebi Laboratory, Iran).

After preparation, formulations were checked for uniformity and the ointment texture, which was utterly consistent and homogeneous, without creating a rough feeling on the skin and no unpleasant odor.

It should be noted that there are not any apparent differences (such as color or consistency) between placebo and whey protein formulations.

Statistical analysis

Descriptive and statistical analyses were performed by SPSS version 20 (IBM Corporation) software. The Shapiro-Wilk Test assessed normality distributions of continuous variables, and related data were reported as mean ± standard deviation or median (IQR1–IQR3) according to distribution. Frequencies of categorical variables were presented, and any association between categorical variables and study groups was examined using Chi-squared or Fisher's exact test. We performed the independent t-tests or Mann–Whitney U test to analyze differences in continuous variables for parametric and nonparametric variables, respectively. Repeated measures analysis of variance examined the PU scores' changing during the study. Moreover, any confounding factor was considered as a covariate during analysis.

Results

Among 192 patients assessed for inclusion and exclusion criteria in the study, 80 were eligible to enroll and were randomly allocated to whey protein and placebo groups after filling out their informed consent forms [Figure 1].

The mean age of patients was 61.2 ± 18.52 years and 60% were male. About half of the patients were admitted to the ICU because of internal medicine complications. There were no significant differences between the study groups in the baseline demographic and clinical characteristics ($P > 0.005$), despite the baseline SOFA score being significantly higher in the intervention group ($P = 0.003$) [Table 1]. Therefore, the SOFA score was considered the confounding factor in repeated measure analysis.

According to the Braden scale, 82.5% of enrolled patients were at least at high risk for developing PUs. The risk of developing PUs according to the Braden tool was on average 2.02 ± 0.73 (median = 2, extremes = 1.25–3) in the placebo group and 2.22 ± 0.70 (median = 2, extremes = 2–3) in the protein whey group, which was not statistically different ($P = 0.168$).

Our findings revealed that all patients in the placebo group developed PUs. In contrast, its incidence in the intervention group was 57.5% during our study (incidence rate = 41.1 and 71.4 PUs × 1,000 patients/day, respectively), which significantly declined based on Fisher's exact test ($P < 0.001$).

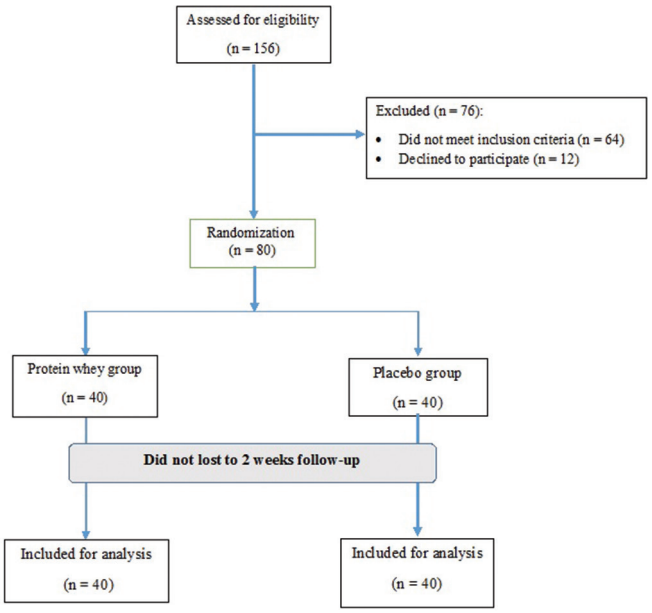

Figure 1: Consort flow diagram of participants in two groups of the study

Analysis of variance in repeated measures of PUSH score from baseline to days 4, 7, and 14 of the study showed a significant difference between groups ($P < 0.001$). Differences in mean scores between groups were 3.1, 4.2, and 6.15 on days 4, 7, and 14 of the study. We observed a higher PUSH score in the placebo group than in the whey protein group at 4, 7, and 14 days of follow-up ($P < 0.001$) [Table 2].

We also reported that the score of PUs did not significantly alter from day 4 to 14 in repeated measure analysis conducted within the placebo group ($P = 0.282$). Analyses of variance showed that the PUSH score increased dramatically from day 4 to 14 in the intervention group ($P < 0.001$).

Moreover, no adverse reactions related to our intervention were detected during the patients' follow-up.

Discussion

The present study results indicated that using the topical formulation of whey protein 2% (w/w) significantly reduced the incidence and the PUSH score of PUs at days 4, 7, and 14 in the intervention group compared to the placebo group. Also, the PUSH scores at these times were significantly lower in the intervention group than in the placebo group. These findings confirmed the potential protective role of whey protein in the healing process.

Frequent and appropriate patient repositioning, proper padding at pressure points, adequate nutrition, and keeping the skin clean and dry are primary preventive strategies to alleviate the risk factors for PU development. Various new dressings have been developed for PU treatment reviewed in the recent study without significant differences in effectiveness.[15-17] Additional

Table 1: Baseline demographic and clinical characteristics in the study groups

Variables	Study groups		*P*
	Placebo group (*n*=40)	Intervention group (*n*=40)	
Sex (male), *n* (%)	26 (65)	22 (55)	0.361*
Age (years), median (IQR)	64 (41-77)	66 (51-77)	0.634**
Cause of ICU admission, *n* (%)			
Trauma	11 (27.5)	16 (40)	0.464*
Surgery	6 (15)	6 (15)	
Medical	23 (57.5)	18 (45.0)	
Underlying disease, *n* (%)			
CHD	5 (12.5)	3 (7.5)	0.712*
Hypertension	0	1 (2.5)	1.000*
kidney disease	4 (10)	7 (17.5)	0.518*
Lung disease	6 (15)	4 (10.5)	0.737*
Baseline SOFA score, median (IQR)	5 (4-6.75)	6.5 (5-8)	0.003**
Smoking, *n* (%)	0	4 (10)	0.116*
Braden score, median (IQR)	11 (9-12.75)	11 (9-12)	0.168**
Risk of developing PU based on Braden tool, *n* (%)			
Low	0	1 (2.5)	0.148*
Moderate	10 (25)	3 (7.5)	
High	19 (47.5)	22 (55)	
Very High	11 (27.5)	14 (35)	

* *P* values are based on the Chi-squared test or Fisher's exact test. ** *P* values are based on Mann-Whitney Test

Table 2: Comparing pressure ulcers scores at different times in study groups

Variables		Groups		*P*
		Placebo (*n*=40)	Intervention (*n*=40)	
PUSH score of pressure ulcer, median (IQR)	Day 4	3 (2.25-4)	0 (0-0)	<0.001*
	Day 7	6 (5-8)	2 (0-3)	<0.001*
	Day 14	9 (7.25-9)	3 (0-4)	<0.001*
	*P***	0.282	<0.001	
	*P****		<0.001	
The category of pressure ulcer surface (cm^2), *n* (%)				
No Sore	Day 4	6 (15)	40 (100)	<0.001#
<0.3		4 (10)	-	
0.3-0.6		16 (40)	-	
0.7-1		10 (25)	-	
1.1-2		4 (10)	-	
No Sore	Day 7	1 (2.5)	17 (42.5)	<0.001#
<0.3		5 (12.5)	9 (22.5)	
0.3-0.6		1 (2.5)	8 (20)	
0.7-1		10 (25)	4 (10)	
2.1-3		7 (17.5)	2 (5)	
3.1-4		9 (22.5)	-	
4.1-8		7 (17.5)	-	
No Sore	Day 14	-	17 (42.5)	<0.001#
<0.3		-	2 (5)	
0.3-0.6		-	11 (27.5)	
0.7-1		1 (2.5)	5 (12.5)	
2.1-3		8 (20)	4 (10)	
3.1-4		9 (22)	1 (2.5)	
4.1-8		12 (30)	-	
8.1-12		8 (20)	-	
12.1-24		2 (5)	-	

* Mann-Whitney *U*, ** Repeated measures ANOVA tests of within groups, *** Repeated measures ANOVA tests of between groups, #*P* values are based on Chi-squared or Fisher's exact test

research is required to introduce more effective products to prevent and treat PUs.[16]

There is no previous study for topical whey protein, but some data supported the topical use of cow's low-fat milk for wound healing in animals.[7,18] Hemmati *et al*.[7] observed that using 5% cow's low-fat milk lyophilized ointment in a rabbit model increased wound healing rate, collagen fibers, and fibroblasts and showed reduced inflammatory cells. It seems that the whey protein component of cow's milk could have a crucial role in the wound healing process. Considering nearly 4% protein in cow's milk, at least 0.5% whey protein ointment seemed to be effective. In recent years, another animal study also reported that dressing wounds in rabbits with 3% fat cow's milk could effectively reduce burn wounds.[18]

Protein is the raw material for repairing tissue cells and is necessary for restoring epithelial tissue.[19] Whey protein, the highest quality protein, is rich in the amino acids cysteine and methionine, which enhance immune functions.[20,21] Therefore, the whey protein component of cow's milk could have a crucial role in the wound healing process. Some data supported the beneficial effect of systemic intake of sufficient protein on the healing process. Gutman and Kongshavn reported that taking whey protein oral supplements for 180–120 days can improve pressure injury in patients.[22] Another study in 2017 described that 14 days of feeding rats with 20% whey protein reduced healing time and reduced PU level.[19] Other clinical and animal studies conducted for the same objective also declared whey protein supplementation's effect on improving ulcers' healing attributed to increased intracellular glutathione synthesis as an antioxidant and modulating inflammation to create a suitable environment for regeneration and recovery.[9,23-26]

This is the first time that the clinical effects of topical whey protein have been evaluated. The topical administration of interventions is safer than its systemic administration. In addition, dressings can accelerate wound healing by closing the wound, preventing tissue damage, reducing edema, and creating a moist environment for epithelial cells to move.[18]

We reported a higher incidence rate of PU compared to the previous studies. It may be related to the higher underlying PU's risk factors in our population. In fact, more than two-thirds of our population were at high risk for developing PUs based on Braden scoring.

Our study was limited because we did not report some possible confounders of the wound healing process, such as pre-albumin, CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), heart failure, and hemodynamic instability.

Conclusion

In this study, we introduced efficient and safe intervention to prevent PUs; however, our results are mostly limited to high-risk patients to develop this injury and the anatomical pressure point of the sacrum. Therefore, more study is required to evaluate the efficacy of topical whey protein on the larger population at different pressure points of the body and those with a lower risk for developing PUs.

Acknowledgments

This study was financially supported by the Isfahan University of Medical Sciences, Isfahan, I.R. Iran through Grant No. deleted for blinded article.

Financial support and sponsorship

Isfahan University of Medical Sciences funded this research study (Grant No. 398227).

Conflicts of interest

There are no conflicts of interest.

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