Impact of a Nutritional Formula Enriched in Fish Oil and Micronutrients on Pressure Ulcers in Critical Care Patients

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Background Pressure ulcers are an important source of morbidity and suffering for patients and a formidable burden on caregivers.
Objectives To assess the impact of a feeding formula enriched with fish oil on healing of preexisting pressure ulcers and serum levels of C-reactive protein in critical care patients.
Methods Adult patients with pressure ulcers grade II or higher were randomly allocated to receive either a formula enriched with fish oil or an isocaloric control formula. Wound healing was assessed by using the Pressure Ulcer Scale for Healing tool on days 7, 14, and 28. Blood levels of C-reactive protein were measured on days 0, 7, and 14.
Results Baseline demographics did not differ between the study (n = 20) and the control (n = 20) groups. The mean score on the ulcer healing tool increased significantly ($P = .02$) from day 0 to day 28 in the control group (from 9.25 [SD, 2.12] to 10.75 [SD, 3.41]) compared with the study group (from 9.10 [SD, 2.84] to 9.40 [SD, 3.72]). Mean levels of C-reactive protein decreased significantly ($P = .02$) from day 0 to day 14 in the study group (from 191 [SD, 104.4] mg/L to 111.7 [SD, 97.8] mg/L) compared with the control group (from 145 [SD, 90] mg/L to 139 [SD, 62] mg/L).
Conclusion Administration of a feeding formula enriched with fish oil was associated with decreased progression of pressure ulcers and a decrease in blood concentrations of C-reactive protein. (*American Journal of Critical Care.* 2012;21:e102-e109)

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A pressure ulcer (decubitus ulcer or bed sore) is an area of localized damage to the skin and underlying tissue caused by pressure, shear, friction forces, or a combination of these. The lesions are a marked source of morbidity and suffering for patients and a formidable burden on caregivers.[1-3] The prevalence of pressure ulcers varies widely, depending on both patient factors (eg, age, physical impairments) and the treatment setting. These ulcers are due to local breakdown of soft tissue caused by compression between a bony prominence and an external surface.[1,2] Ongoing mechanical pressure, which reduces cutaneous perfusion, and friction or shear forces act in concert to promote tissue breakdown and necrosis of muscle, subcutaneous tissue, dermis, and epidermis, with the consequent formation of pressure ulcers. These mechanical factors, as well as systemic factors, may impair wound healing, thereby contributing to the persistence of pressure ulcers.[2]

Intensive care unit (ICU) patients are particularly predisposed to pressure ulcers because of several risk factors, including infusions of norepinephrine, scores greater than 13 on the Acute Physiology and Chronic Health Evaluation II, frequent fecal incontinence, anemia, and prolonged ICU stay. In addition, immobility, disturbed sensory perception,[4] and malnutrition, which hampers immune function and wound healing, also increase the risk for pressure ulcers.[4,5]

In a recent study[6] in patients with acute lung injury, those who received an enteral nutritional formula enriched with fish oil containing ω-3 light-chain polyunsaturated fatty acids (PUFAs) and micronutrients had greater improvement in oxygenation than did those who received an isocaloric control formula. The improvement in pulmonary function was attributed to the established anti-inflammatory property of the ω-3 light-chain PUFAs and micronutrients. Furthermore, the incidence of new pressure ulcers was significantly reduced by use of the specialized formula.[7] This important finding led us to speculate that this formula might also aid in the healing of new pressure ulcers in the general ICU population. We hypothesized that attenuation of inflammation by the formula would help maintain the immune processes involved in wound healing.

The objective of this clinical trial was to assess the effect in ICU patients of a formula enriched in eicosapentaenoic acid and micronutrients on the healing of existing pressure ulcers and on acute inflammation as indicated by serum levels of C-reactive protein (CRP).[8]

> Fish oil enriched formula with anti-inflammatory properties improved oxygenation in patients with acute lung injury.

Methods

Patients

This interventional, controlled, randomized study was conducted in a 12-bed general ICU of the Rabin Medical Center, Petah Tikva, Israel, a tertiary care, university-affiliated hospital. The sample consisted of all adult patients admitted to the ICU who were expected to require nutritional support for at least 5 days and who had evidence of grade II or higher pressure ulcers (ie, damage of the epidermis extending at least into the dermis), according to the classification of the National Pressure Ulcer Advisory Panel,[1] that were present either at the time of admission to the ICU or developed during the ICU stay. Exclusion criteria included conditions associated with markedly impaired immunity and/or wound healing, such as AIDS, autoimmune disorders, and treatment with immunosuppressive medications. The study design

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Table 1
Composition of selected nutrients in 100 mL of the control and study formulas

Nutrient	Control formulas		Study formulas	
	Enteral[a]	Parenteral[b]	Enteral[c]	Parenteral[d]
Carbohydrates, g	15.4	14.1	10.5	14.1
Fat, g	3.5	4.0	9.4	4.0
Protein, g	4.4	3.4	6.2	3.4
Eicosapentaenoic acid, g	0	0	0.46	0.125-0.282
Docosahexaenoic acid, g	0	0	0	0.144-0.309
γ-Linoleic acid, g	0	0	0.4	0
Vitamin C, mg	15.7-22.5	125	850	125
Vitamin E, IU	2.3-3.4	1.12	32.0	1.12
Vitamin A, IU	375.9	350.0	667.8[e]	350.0
Copper, mg/L	1-1.5	0.4	2.2	0.4
Manganese, mg/L	2.6-3.7	0.1	5.3	0.1
Zinc, mg/L	16.8	1	23.9	1

[a] Jevity (Abbott Nutrition, Columbus, Ohio).
[b] OliClinomel N6-990 E (Baxter Healthcare Ltd, Maurepas, France).
[c] Oxepa (Abbott Nutrition, Columbus, Ohio).
[d] OliClinomel N6-990 E (Baxter Healthcare Ltd, Maurepas, France) and Omegaven (Fresenius Kabi, Bad Homburg, Germany).
[e] Supplied by 5 mg of beta carotene.

was approved by the appropriate institutional internal review board, and informed consent was obtained from all patients before their enrollment.

Study Treatments

Eligible patients were randomly allocated to 2 groups according to a computer-generated random list: the study group, which received an enteral nutritional formula enriched in fish oil and antioxidants (Oxepa, Abbott Nutrition, Columbus, Ohio) and the control group, which received an isonitrogenous nutritional formula (Jevity, Abbott Nutrition). Patients who could not tolerate enteral nutrition (as indicated by a gastric residual volume >500 mL) received parenteral nutrition in the form of OliClinomel N6-900 (Baxter Healthcare Ltd, Maurepas, France). Patients in the study group who required parenteral nutrition also received Omegaven (Fresenius Kabi AG, Bad Homburg, Germany) as the source of fish oil. Table 1 gives the macronutrient and micronutrient composition of the various formulas. Treatment allocation was concealed from the study statistician but not from ICU staff, patients, or the assessor of ulcer severity.

Patients with grade II or higher pressure ulcers were enrolled.

The quantity of nutritional formula prescribed was determined on the basis of the nonfasting resting energy expenditure, as measured by indirect calorimetry (Deltatrac II, Datex-Ohmeda, Helsinki, Finland). Resting energy expenditure was assessed every 7 days, and the calorie prescription was adjusted as needed. Assessment of gastric residual volume and the consequent adjustment of nutritional support were performed according to established ICU protocols. Glucose levels were monitored every hour, and, when necessary, patients received a continuous infusion of insulin; the goal was to maintain the glucose level between 60 and 150 mg/dL (to convert to millimoles per liter, multiply by 0.0555). All other aspects of patient management were determined by each patient's attending physician. Treatment regimens for grade II pressure ulcers for all patients consisted of hydrogel dressings (Granuflex, ConvaTec Ltd, Ickenham, United Kingdom) when secretions were minimal, alginates (Kaltostat, ConvaTec Inc, Skillman, New Jersey, or SeaSorb, Coloplast, Minneapolis, Minnesota) when secretions were moderate, and specialty absorptives (Kaltostat, ConvaTec Inc, Skillman, New Jersey) when secretions were excessive. Treatment regimens for grade III pressure ulcers consisted of composite dressings (TenderWet, Paul Hartmann AG, Heidenheim, Germany).

Outcomes and Data Collection

Effectiveness of treatment was defined as the degree of progression of existing pressure ulcers.

The following data were collected for all patients at the time of admission to the ICU: sex, age, body mass index (calculated as weight in kilograms divided by height in meters squared), primary diagnosis (surgical, medical, or trauma), and score on the Acute Physiology and Chronic Health Evaluation (APACHE) II. The amount of enteral formula, kilocalories, protein, and PUFAs delivered and energy balance (calories delivered daily minus resting energy expenditure measured weekly) were recorded on a daily basis. CRP concentrations were recorded weekly. CRP was assayed by using an Olympus 2700 Analyzer and a particle-enhanced immunoturbidimetric method with latex particles coated with monoclonal antibodies to CRP. The day-to-day variation for the measurement is 3.04% at 14.1 mg/L, 2.51% at 27.7 mg/L, and 1.18% at 0.83 mg/L (multiply by 9.524 to convert to nanomoles per liter). The test is linear within a concentration range of 0.08 to 80 mg/L, and the reference interval is less than 5 mg/L.

The severity of pressure ulcers at baseline (day 0), and the response to treatment (on days 7, 14, and 28) were assessed by using the Pressure Ulcer Scale for Healing (PUSH) tool.[9] With this noninvasive diagnostic tool, severity scores range from 0 (healed) to 17 (worst possible score). The score is a summation of 3 parameters, each of which is graded according to increments in severity: surface area, which is measured with a ruler designed for this purpose (0-10 points); amount of exudate (0-3 points: none, light, moderate, or heavy); and tissue type (0-4: closed, epithelial tissue, granulation tissue, sloughing, or necrotic tissue). The changes in the direction and magnitude of the score over time provide a validated indication of whether or not the wound is healing. The PUSH score was obtained by a single investigator (M.T.) in all patients. When a patients had more than 1 pressure ulcer, only the largest ulcer with the most exudation was assessed in the study.

Data Analysis

On the basis of the study of Makhsous et al,[10] the standard deviation of the change in the PUSH score can be estimated at 1.8. The difference in mean improvement between the groups in their study[10] was also 1.8. In our study, a sample size of 40 was deemed sufficient to detect such a difference with a power of approximately 85%. Differences in baseline data and patient characteristics were assessed by using Wilcoxon and independent *t* tests for nonparametric and parametric variables, respectively. The changes in the severity of pressure ulcers to treatment were analyzed by using repeated-measures analysis of variance. Data were analyzed by using SPSS 17 for Windows (IBM SPSS, Armonk, New York). Results were considered significant at $P < .05$.

Table 2
Characteristics of patients in the study

Characteristic[a]	Control group	Intervention group
No. of patients	20	20
Age, mean (SD), y	53.1 (19.3)	49.3 (20.7)
Sex, male/female	13/7	14/6
Body mass index,[b] mean (SD)	32.1 (9.9)	28.3 (4.8)
Hours in intensive care unit, mean (SD)	507.0 (217.8)	627.2 (340.9)
APACHE II score, mean (SD)	25.7 (7.0)	23.0 (6.7)
Diagnostic category		
Medical	9	5
Trauma	8	11
Surgery	3	4

Abbreviation: APACHE, Acute Physiology and Chronic Health Evaluation.
[a] No significant differences were noted between the 2 groups for any characteristic.
[b] Calculated as the weight in kilograms divided by the height in meters squared.

Results

Characteristics of the Sample

A total of 40 patients, 20 in each treatment arm, were enrolled in the study. All patients completed at least 7 days of enteral or parenteral nutrition therapy and were therefore eligible for the intention-to-treat analysis. A total of 2 patients in the control group and 1 patient in the study group had a visible pressure ulcer at the time of admission to the ICU; in the remaining patients ulcers developed after a mean of 6.7 days (SD, 2.1) in the control group and 6.1 days (SD, 2.0) in the study group. These differences were not significant ($P = .07$). Patients in the 2 groups did not differ significantly in age, body mass index, proportion of men and women, diagnostic category, or scores on the APACHE II (Table 2). In each group, 5 patients had preexisting type 2 diabetes mellitus.

The treatment group had greater decreases in C-reactive protein levels.

Study Treatments

Nutritional data are summarized and presented in Figure 1. Mean energy requirements (as reflected by resting energy expenditure) and daily kilocalorie intake did not differ significantly between the 2 groups ($P = .37$). The number of patients who received enteral nutrition or parenteral nutrition in each group and the duration of nutritional support are depicted in Figure 1. The contribution to the energy load

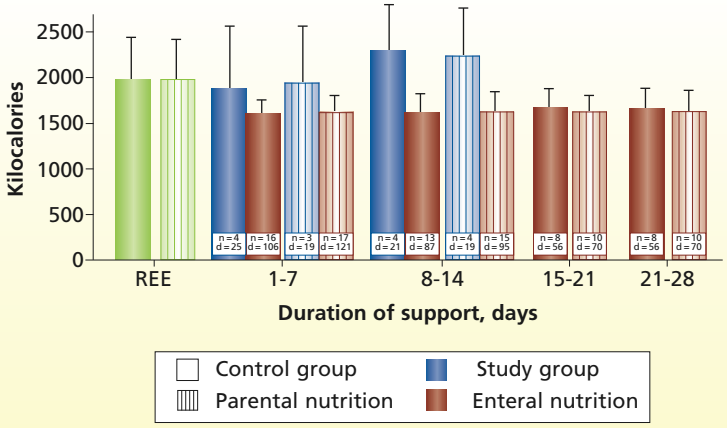

Figure 1 Number of patients in each group who received enteral or parenteral nutrition and duration of support. d, number of days; n, number of patients; REE, resting energy expenditure.

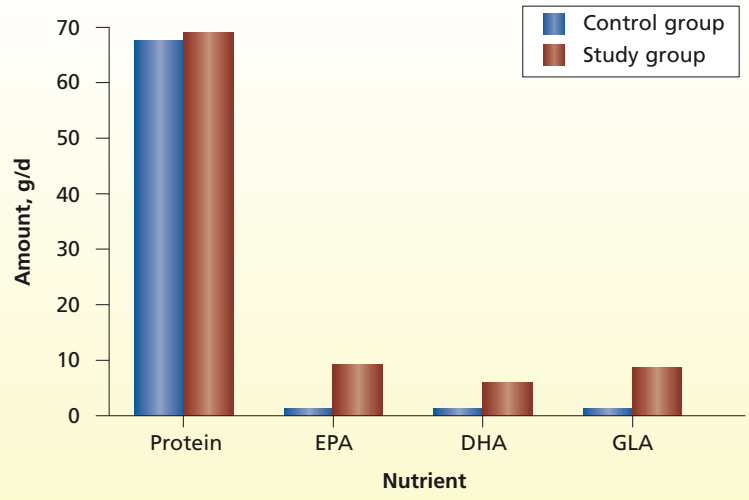

Figure 2 The amount of protein and added fatty acids (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], and γ-linoleic acid [GLA]) administered to patients in the 2 treatment groups. The amounts of all 3 fatty acids (but not the amounts of protein) differed significantly ($P < .001$) between control and study groups.

from added protein and fatty acids is shown in Figure 2. Protein intake did not differ significantly between the 2 groups.

Outcome Data

On enrollment, the severity of pressure ulcers did not differ significantly ($P = .02$) between the control group (mean score, 9.25; SD, 2.12) and the study group (mean score, 9.10; SD, 2.84; Table 3). The grade of the pressure ulcers at enrollment also did not differ significantly ($P = .02$) between the control group (grade II in 13 patients and grade III in 7 patients) and the study group (grade II in 14 patients and grade III in 6 patients) During the study, the severity of pressure ulcers, as indicated by the PUSH score, increased significantly for the control group ($P = .02$) but not for the study group. Decreases in CRP concentrations (Table 4) were significantly greater in the study group than in the control group ($P = .02$).

Discussion

In this study, ICU patients who received nutritional support enriched with fish oil (eicosapentaenoic acid) and micronutrients had significantly less progression of existing pressure ulcers than did patients who received an isonitrogenous, nutrient-sufficient formula. In addition, decreases in CRP concentrations were greater in the study group than in the control group.

Wound healing refers to the complex and dynamic process of restoring cellular structures and tissue layers after injury and/or infection. The wound healing process in humans can be divided into 3 phases: inflammatory, proliferative, and remodeling.[11] The role of the initial inflammatory phase is isolation and removal of the injurious or infectious agent and removal of cellular debris (endogenous debridement) before tissue reconstruction. The reparative stages (ie, the proliferative and remodeling phases), involve a shift in the predominant cellular activity from phagocyte-mediated inflammation and catabolism to epithelial and mesenchymal anabolic processes. In the proliferative phase, fibroblasts, smooth muscle cells, and endothelial cells infiltrate the wound as epithelial cells begin to cover the site of injury. Finally, the collagen matrix continually undergoes reabsorption and deposition to remodel and strengthen the wound, constituting the remodeling phase of healing.[12,13]

Thus, healing of significant wounds is a metabolically demanding process, requiring considerable quantities of calories and amino acids.[1,5,14] Continuous administration of calories and protein is also important for appropriate wound healing in acute illness.[15] In our study, both groups of patients received similar and adequate amounts of protein and calories to support wound healing. Nevertheless, the effect on pressure ulcers occurred solely in patients who received the nutritional formula enriched with eicosapentaenoic acid and micronutrients. We did not assess the specific contribution of the multivitamins and minerals. Interestingly, we previously showed that the use of the same nutritional formula in critically ill patients with acute respiratory distress syndrome did not result in higher serum levels of vitamins.[7]

Although the inflammatory phase is an essential physiological response,[16] excessive release of

proinflammatory molecules may exacerbate tissue injury. Indeed, the depiction of inflammation as a double-edged sword, as in response to infection,[17] is also applicable to wound healing.[18] Several lines of evidence support the notion that self-resolving inflammation is a normal and necessary prerequisite to fibroblast activation and net matrix synthesis, whereas an inflammatory response that is excessive in magnitude and duration hampers the transition from the inflammatory phase to the reparative phases of tissue repair.[12,18] Impaired healing of chronic venous ulcers,[19] wounds associated with diabetes,[20] and trauma-induced wounds[21] may be attributed in part to an injurious inflammatory response.

In our study, the interventional nutritional formula prevented progression of pressure ulcers and was associated with reduced concentrations of the acute-phase reactant CRP. Previous studies[22] have shown that supplementation with ω-3 acids results in decreases in CRP levels. Thus, supplemented parenteral nutrition resulted in a decrease in CRP levels in severe acute pancreatitis and was associated with a decrease in the hyperinflammatory response and attenuation of systemic disease sequelae.[22] In addition, fish-oil supplementation lowered CRP levels in patients with end-stage renal disease.[23] Although our findings do not firmly establish a causative association, the temporal sequence of these effects suggests that ω-3 PUFAs may have attenuated the inflammatory response in a manner that minimizes tissue injury while avoiding suppression of those components of inflammation necessary for subsequent wound healing. Dampening the magnitude of the inflammatory response might facilitate resolution of inflammation and transition to wound healing. Indeed, novel lipid mediators derived from ω-3 PUFAs, the resolvins and protectins, promote the resolution of inflammation. These mediators are synthesized during the later stages of inflammation (ie, after the classic eicosanoids), at which time they enhance macrophage engulfment of apoptotic neutrophils and the efflux of macrophages to local lymph nodes.[24,25] Recently, resolvins were shown to enhance resolution of inflammation and microbial clearance in experimental critical illness.[26] Thus, ω-3 PUFAs have pleiotropic properties during inflammation through production of weaker eicosanoids (eg, leukotriene B_5 vs leukotriene B_4), inhibition of nuclear factor κB, and direct promotion of resolution.[27] Determining whether resolvins and protectins directly induce the wound-healing macrophage phenotype would be of interest.

In addition to its content of long-chain ω-3 PUFAs, our study formula contained higher concentrations of certain micronutrients, some of which are operative in wound healing, than did the control formula. However, on the basis of the micronutrient dose necessary to improve wound healing in supplementation trials,[7] most likely the quantitive difference in micronutrients was insufficient to facilitate tissue

Table 3
Subscores and scores on Pressure Ulcer Scale for Healing

Variable	Day	Score, mean (SD)		*P*
		Control group	Study group	
Length x width[a]	0	5.63 (1.76)	6.30 (2.00)	.07
	7	6.00 (1.85)	6.30 (2.62)	
	14	6.63 (1.99)	6.10 (2.42)	
	28	6.75 (2.25)	6.00 (2.79)	
Exudate amount[b]	0	1.25 (0.46)	1.40 (0.96)	.02
	7	1.38 (0.74)	1.20 (0.78)	
	14	1.50 (0.75)	1.20 (0.78)	
	28	1.63 (0.74)	1.20 (0.79)	
Tissue type[c]	0	2.38 (0.74)	2.60 (0.96)	.65
	7	2.38 (0.74)	2.50 (0.70)	
	14	2.25 (0.70)	2.30 (0.82)	
	28	2.38 (0.74)	2.30 (0.82)	
Total score[d]	0	9.25 (2.12)	9.10 (2.84)	.02
	7	9.44 (2.60)	8.79 (3.39)	
	14	9.67 (2.50)	9.19 (4.10)	
	28	10.75 (3.41)	9.40 (3.72)	

[a] Length × width is defined by 0 points if 0 cm^2,1 point if <0.3 cm^2, 2 points if 0.3-0.6 cm^2, 3 points if 0.7-1.0 cm^2, 4 points if 1.1-2 cm^2, 5 points if 2.1-3 cm^2, 6 points if 3.1-4 cm^2, 7 points if 4.1-8 cm^2, 8 points if 8.1-12 cm^2, 9 points if 12.1-24 cm^2, 10 points if >24 cm^2.
[b] Exudate amount is defined as follows: 0 if none, 1 if light, 2 if moderate, and 3 if heavy.
[c] Tissue type is defined as 0 points if closed,1 point if epithelial tissue is present, 2 points if granulation tissue is present, 3 if slough is present, and 4 if necrotic tissue is present.
[d] $P < .05$, study vs control group as calculated by using repeated-measures analysis of variance.

Table 4
Concentrations of C-reactive protein during the 14-day study period

Day	C-reactive protein, mg/L	
	Control group	Study group
0	145 (90)	191 (104.4)
7	149 (81)	105[a] (85.6)
14	139 (62)	111.7[b] (97.8)

[a] Length × width is defined by 0 points if 0 cm^2,1 point if <0.3 cm^2, 2 points if 0.3-0.6 cm^2, 3 points if 0.7-1.0 cm^2, 4 points if 1.1-2 cm^2, 5 points if 2.1-3 cm^2, 6 points if 3.1-4 cm^2, 7 points if 4.1-8 cm^2, 8 points if 8.1-12 cm^2, 9 points if 12.1-24 cm^2, 10 points if >24 cm^2.
[b] Exudate amount is defined as follows: 0 if none, 1 if light, 2 if moderate, and 3 if heavy.
[c] Tissue type is defined as 0 points if closed,1 point if epithelial tissue is present, 2 points if granulation tissue is present, 3 if slough is present, and 4 if necrotic tissue is present.
[d] $P = .02$, study vs control group as calculated by using repeated-measures analysis of variance.

repair independently of fish oil. However, a synergistic cytoprotective and anti-inflammatory effect is possible, and antioxidant nutrients are vital to prevent PUFA peroxidation. The relative roles of ω-3 PUFAs and individual micronutrients in promoting healing of pressure ulcers therefore requires further research.

Of note, the cost of the study formula (enteral and parenteral components) was significantly higher for the study group ($99.60/d) than for the control group ($44.20/d). However, pressure ulcers are a major burden on health care systems.[28] Thus, the costs of treatment of pressure ulcers in the United States are on the order of $500 to $40 000 per ulcer, depending on the stage of the ulcer.[28] In the United Kingdom, the total cost for a patient with a full-thickness ulcer has been estimated at £30 000 (€36 376).[28] Finally, an Australian study[28] indicated that in 2001 to 2002, costs for bed days lost were a median of AU $285 million in Australian public hospitals. We did not perform a cost analysis in our study. However, these figures for other countries suggest that an intervention, such as ours, that decreases the incidence of pressure ulcers may have an important economic impact and negate the added costs of the intervention.

In wound healing excessive release of proinflammatory molecules may exacerbate tissue injury.

Although our clinical and laboratory end points were significant, our study has several limitations. All assessments of pressure ulcers were completed by a single investigator, a situation that might have introduced an element of bias. Treatment allocation was known by the participants and some of the care providers, and the study included a relatively small number of patients. For example, the investigator who assessed ulcer severity knew the allocation because he is an active member of the ICU staff.

Our patients, in both groups, received 80% of their measured energy requirements via the enteral route. This route was used largely because of technical reasons and has been described by others.[27] On the other hand, the target was achieved for patients receiving parenteral nutrition. Finally, we did not firmly establish a causative association between the anti-inflammatory effect of the formula and the subsequent improvement in pressure ulcer status. Larger clinical trials are necessary to establish whether the presence of grade II pressure ulcers may benefit from enriched nutrition in the ICU.

Dampening the inflammatory response might facilitate transition to wound healing.

Conclusion

In conclusion, our results suggest that the addition of fish oil to the nutritional regimen of critically ill patients in the ICU may slow the progression of pressure ulcers, as indicated by the PUSH score. The slowing in progression was associated with a decrease in the levels of CRP, suggesting the effect was mediated by anti-inflammatory mechanisms. Studies that include assessment of tissue physiology are warranted to determine the mechanisms by which fish oil and micronutrients may facilitate wound healing.

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None reported.

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