MJMR, Vol. 33, No. 2, 2022, pages (220-227).

Open Access
ISSN:2682-4558

Research Article

Protein Supplementation during Critical Illness in ICU

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Abstract
Background: Inadequate supply of protein and energy results in malnutrition. Critically ill patients have high energy expenditure and consequently, require high energy nutrition, also they lose muscle, besides the effects of a procatabolic hormones and cytokines. This study aimed to evaluate the impact of proteins' supplementation during the critical illness of patients in ICU, on muscle thickness (cm) on ultrasound, ventilator need, and two-month mortality. **Methods:** Our prospective comparative study involved 60 cases who were suffering from acute critical illness and had parenteral nutrition during their ICU stay. The patients were divided into 2 groups; a standard protein group who received a protein concentration of 1 g/kg/day (Group A) and a high protein group who received a protein concentration of 2 g/kg/day (Group B). The nutrition was delivered through a central line and separate bottles technique. **Results:** The muscle thickness of the forearm and thigh, besides overall muscle thickness, was significantly higher in group B on day 7. The duration of mechanical ventilation was not significantly different between both groups. The protein dose was not significantly associated with overall two-month mortality. **Conclusion:** The supplementation of 2 g/kg/day of protein parenterally, exhibited significant improvement of muscle thickness, ventilator need, and mortality rates. Studies with larger sample size and longer duration of follow-up are recommended.

Key words: ICU, malnutrition, procatabolic hormones and cytokines

Introduction
Severe sickness is distinguished by a decrease in total body protein mass, mostly from the skeletal muscle. Protein turnover refers to an increase in protein degradation as well as, to a lesser extent, an increase in whole-body protein synthesis[(1)]. Insulin resistance, faster proteo-lysis, and enhanced glutamine and other amino acid release are all examples of skeletal muscle adaptation to severe disease. This amino acid outflow from skeletal muscle offers precursors for protein synthesis as well as energy fuel to the liver, as well as rapidly proliferating cells of the intestinal mucosa and the immune system. These adaptive processes result in significant muscle wasting, glutamine depletion, and hyperglycemia, as well as increased morbidity and death in patients [(2)].

Protein prescriptions are based on the goal of reducing the breakdown of muscle proteins into amino acids, which serve as the substrate for gluconeogenesis and are reflected in a positive nitrogen balance[(3)]. Exogenous glucose cannot completely reduce amino acids produced by skeletal muscle breakdown during severe illness. The complicated stress response helps explain some of this behavior. As a result, it was concluded that the introduction of exogenous protein might generate a protein-sparing effect in critically sick patients by stimulating protein synthesis[(4)]. When a patient is unstable, it is customary for parenteral nourishment to be administered around the clock. The requirement for 24-hour infusion should be reconsidered as soon as feasible, with the infusion time gradually reduced to 16–18 hours each day[(5)]. If EN is not achievable in patients with pre-existing protein-calorie malnutrition (PCM), parenteral nutrition should be started as soon as possible[(6)].

Anabolism outnumbers catabolism during recovery from critical illness. Nutritional support serves as a substrate for the anabolic state, which occurs when the body corrects hypoproteinemia, repairs muscle loss, and refills other nutritional resources [(7)]. Diseases characterized by severe catabolism, such as muscular wasting in advanced lung illness, are

likely the result of a combination of inadequate diet, deconditioning, age, and, in some cases, medicine (e.g. oral glucocorticoids). Despite their traditional impact of increasing appetite, glucocorticoids, which are commonly used to treat COPD exacerbations, play a crucial role in wasting syndromes by blocking protein synthesis and encouraging protein catabolism. The muscle wasting effects of glucocorticoids (also known as glucocorticoid-induced myopathy) appear to be dose-dependent, with dosages more than 60 mg/day causing deficits in respiratory muscular strength and a delay in muscle function recovery for many weeks [8].

Patients and methods

This study was conducted during the period from January 2020 and March 2021in El-Minya University Hospital. Sixty abdominal surgery/trauma ICU patients who have a contraindication or intolerance to enteral nutrition (EN), were fed parenterally within 24-48 hours from admission at our surgical ICU. Patients were divided into two groups at random based on protein administration method. Patients in Group A (n=30) got parenteral proteins at a dose of 1 g/kg/day, whereas patients in Group B (n=30) received parenteral proteins at a dose of 2 g/kg/day. The caloric needs for both groups were set at 25- 30 kcal/kg/d. Patients varied in age from 18 to 70 years old. Any pregnant woman, as well as those with hepatic or renal disease, were excluded. Patients under the age of 18 were likewise barred from participating (as growth alters protein requirement).

Both patients' groups were subjected to: History taking from ICU staff about causes for introducing PN, number of day's admission in ICU, number of day's admission in hospital, and number of days on mechanical ventilator. All PN was delivered through a central venous access device and using separate bottles technique, the 2 solutions were packed identically by the hospital's independent pharmacist and labeled clearly. The protein content (was supplied as 10%), and the remaining energy requirements were distributed between carbohydrates (glucose 25%) and lipids (SMOF 20%) in a 60:40 ratio, with a goal of 30kcal/kg. The muscle thickness of the flexor compartment of the mid-upper arm was measured perpendicularly from the bone to the superficial fat-muscle using diagnostic 2-dimensional ultrasonography. Biceps muscle thickness ultrasound: The patients were supine, with the arm in passive extension and the forearm supinated, with their limbs extended and relaxed.

The ultrasonic probe was held vertically against the skin surface to precisely measure the maximal cross sectional area of the biceps brachii muscle in the dominant hand to 0.01 cm. It was utilized as a marker to assess fat thickness and muscle thickness in its axial view. After a 10-minute pause, the measurement was repeated. The average measurement was taken on days 3 and 7. Ultrasound of the thickness of the forearm muscles: from the interosseus membrane to the superficial fat-muscle interface at the midway of the ulnar length stated above. Thigh muscle thickness and cross-sectional area of the rectus femoris anteriorly at the mid-thigh and two-thirds points indicated above were measured using ultrasound. Participants lay supine, with one leg in passive extension and the other in neutral rotation. All measurements were taken with a multifrequency linear array transducer, unless the patient's limb size required a sector array transducer to properly observe the thigh cross section. Each measurement was made perpendicular to the limb's long axis, with the transducer head perpendicular to the limb surface and minimum dermal surface depression.

Every ultrasound measurements were taken by a same skilled operator, and each scan was analysed and measured individually by a single independent trained ultrasonographer who was blinded to the scan sequence. Reproducibility had previously been determined by repeating the same measurements on three successive days on weight-stable volunteers. The typical coefficients of variation for upper arm, forearm, and thigh muscle thicknesses for this operator were 4.8 percent, 3.9 percent, and 4.1 percent, respectively. Measurements were taken in triplicate and the mean of the three measurements was utilized. The total of the means for the 3 measurement sites was recorded on each of days 0, 3, and 7. Biochemical measurements like serum electrolytes, blood

glucose, lipid profile and a 24-hour urinary collection were performed in patients not on dialysis to evaluate urinary urea, creatinine, and amino acids. Two months mortality was recorded.

Statistical analysis

Analysis of data was performed using SPSS for Windows version 23 for statistical analysis. Description of quantitative variables will be in the form of mean, standard deviation (SD), minimum and maximum. Description of qualitative variables will be in the form of numbers (No.) and percents (%). Data was explored for normality using Kolmogorov-Smirnov test of normality. Parametric tests will be used for most of the comparisons. Comparison between quantitative variables will be carried out by One-way analysis of variance (ANOVA) to test the difference between the means of several subgroups of a variable. Relation between qualitative variables will be carried out by Chisquared test to determine the relationship between two or more classification factors. Binary correlation will be carried out by Pearson correlation test. Results will be expressed in the form of correlation coefficient (R) and Pvalues. The significance of the results will be assessed in the form of P-value that is differentiated into: Non-significant when P-value > 0.05, Significant when P-value ≤ 0.05, or highly significant when P-value ≤ 0.01.

Results

The present prospective comparative study involved 60 cases who were suffering from acute critical illness and had parenteral nutrition during their ICU stay. According to table 1 and Fig. 1, APACHE II score mean was lower in group A compared to group B (21.8±4.9 compared to 22.6±5.9 years respectively) with no statistical significant difference (p value > 0.05). While SOFA score median was nearly equal in both group A and B (8 in both groups) with no statistical significant difference (p value > 0.05), as illustrated in table 1 and Fig. 2. Table 2 showed reason for parenteral nutrition among both studied groups. The most common reason among both groups was abdominal trauma being 43.3% in group A compared to 40% in group B with no statistical significant difference (p value > 0.05).

On study day 7; mean muscle thickness of forearm, thigh and Sum of muscle sites was significantly higher in group B (3.3, 6.7, 8.8) respectively than group A (2.4, 5.9, 7.9), as noticed in table 3. Two-month mortality was 10% in group A compared to 6.7% in group B with no statistical significant difference, as shown in table 4. Table 5 demonstrated that ventilator need was 16.7% in group A compared to 13.3% in group B with no statistical significant difference.

Table (1): APACHE II and SOFA scores among studied groups

Score	Groups				P value
	A		B		
	Mean ± SD	Range	Mean ± SD	Range	
APACHE II	21.8±4.9	10.0:28.0	22.6±5.9	11.0:38.0	0.431
SOFA	7.5±1.1	5.0:9.2	8.0±0.9	6.0:9.4	0.511

SD: Standard Deviation, IQR: Inter Quartile Range

a: p value for independent sample t test b : p value for Mann-Whitney test

Table (2): Nutritional status among studied groups

			Groups		P value
			A	B	
Nutrition status	SGA A	Number	18	22	0.539
		%	60.0%	73.3%	
	SGA B	Number	10	7	
		%	33.3%	23.3%	
	SGA C	Number	2	1	
		%	6.7%	3.3%	
Total		Number	30	30	
		%	100.0%	100.0%	

Fisher's Exact Test, SGA A (acceptably nourished), SGA B (mild/moderately malnourished) SGA C (severely malnourished)

Table (3): Muscle thickness (cm) on ultrasound on study day 3 and 7 among studied groups

Muscle thickness in cm	Groups				P value
	A		B		
	Mean±SD	Range	Mean±SD	Range	
Biceps thickness day3	1.3±0.5	0.6:2.1	1.4±0.5	0.5:2.6	0.215
Biceps thickness day7	1.8±0.5	0.8:3	1.9±0.5	0.9:3.5	0.392
Forearm thickness day3	1.7±0.4	0.9:2.5	1.8±0.5	1:2.9	0.135
Forearm thickness day7	2.4±0.6	1.5:3.6	3.3±0.7	1.9:4.6	<0.001
Thigh thickness day3	5.4±0.2	1.9:4.9	5.8±0.3	2.5:7.5	0.211
Thigh thickness day7	5.9±0.1	2:5.9	6.7±0.3	3:8.6	<0.001
Sum of muscle sites thickness day3	7.8±0.4	3.8:7.9	8.0±0.1	4:7.9	0.611
Sum of muscle sites thickness day7	7.9±0.8	4.9:7.8	8.8±0.7	6.3:8.9	<0.001

SD: Standard Deviation, IQR: Inter Quartile Range, p value for independent sample t test

Table (4): Two-month mortality among studied groups

			Groups		P value
			A	B	
Mortality	No	Number	27	28	1.000
		%	90.0%	93.3%	
	Yes	Number	3	2	
		%	10.0%	6.7%	
Total		Number	30	30	
		%	100.0%	100.0%	

Fisher's Exact Test

Table (5): Ventilator need among studied groups

			Groups		P value
			A	B	
Ventilator need	No	Number	25	26	1.000
		%	83.3%	86.7%	
	Yes	Number	5	4	
		%	16.7%	13.3%	
Total		Number	30	30	
		%	100.0%	100.0%	

Fisher's Exact Test

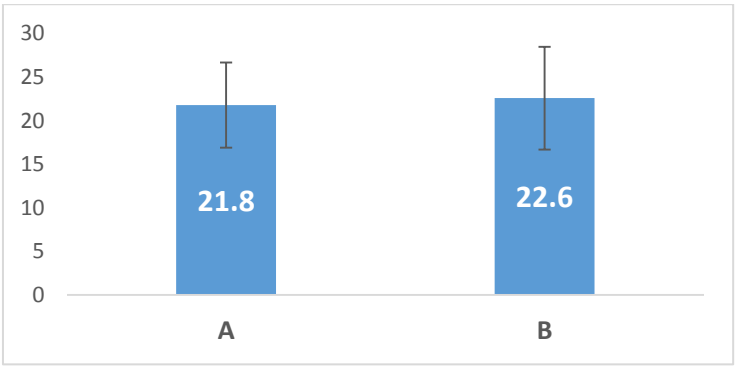

Figure (1): showing the difference between both groups concerning APACHE II scores.

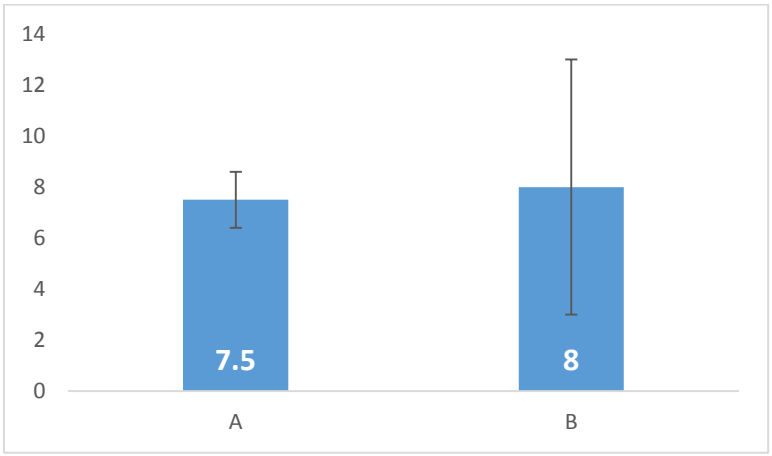

Figure (2): showing the difference between both groups concerning SOFA scores

Discussion

Many negative effects are connected with critical illness. One of the most prevalent is an increase in muscle catabolism. This might be attributed to malnutrition, which is a common documented concern among hospitalized patients, particularly those in the intensive care unit. It is believed that between 20% and 50% of patients admitted to hospitals are malnourished [(9)]. There is an issue with the lack of a defined criteria for malnutrition in ICU patients. The Global Leadership Initiative on Malnutrition (GLIM) attempted to address the issue. They established precise criteria for reliable diagnosis by integrating phenotypic and etiologic parameters: The phenotypic one includes either weight reduction or a decrease in BMI, with a focus on the muscle component. The causative factors include the existence of inflammation or a reduction in food consumption [(10)]. Another problem is that too many people in intensive care units seem unable to live a healthy lifestyle owing to their life-threatening diseases, which frequently reach the level of unconsciousness. As a result, it is regarded as one of the most crucial aspects in most patients' treatment success. Their daily requirements are meticulously estimated based on a precise plan for each patient based on their clinical state and reported outcome [(11)].

The majority of ICU patients acquire systemic inflammatory disorders as a result of their disease. As a result, their bodies experience acute stress and require more metabolic demands [(12)]. To compensate for the fast protein loss, the body reacts in the early stages by consuming massive amounts of amino acids for the synthesis of new proteins within the liver, spleen, and bone marrow. As the length of the sickness increases, the human body begins to utilize fat as a source of energy, first from fat

store and later from muscle protein storage, in order to meet the metabolic demands of the acute stressful circumstances [13]. Consequently, the immune system becomes suppressed and weaker. The wounds take longer time for healing. The length of stay in ICU becomes longer and patients become weaker. So, exogenous proteins should be supplemented to compensate for that loss [14].

As such, we kept an eye on 60 cases with critical illnesses who had recently been admitted to the ICU and required parenteral nutrition to ensure that the protein components of their nutrition met current practice guidelines, which state that protein intake should range between 1.2 and 2.5 g/kg/day [15]. They were divided into two groups; Group A, those patients received parenteral proteins in a dose of 1 g/kg/day and Group B patients received parenteral proteins in a dose of 2g/kg/day. Caloric requirements were fixed at 30 kcal /kg/d for both groups. In our study, we found that decreased protein intake was associated with higher mortality among critically ill patients compared to those with higher doses (10%, 3 patients vs 6.7%, 2 patients) respectively. However, this was statistically insignificant (p=1.00). This was consistent with Arabi et al. who found that no difference was found between low and high protein intake groups [16].
However, the mortality rate in Arabi et al., [16] was much higher than in our study; 24.2% of patients with high protein intake compared to 25.9% of those with low protein intake. This may be due to long follow up period in their study which was 9 months. Similarly, Koekkoek et al., [17] reported a higher mortality rate among patients in both groups (33.3% of high protein group vs 63% of low protein group. This may be due to larger sample size and longer durations of follow up. Looijaard et al., [18] investigated the link between high protein consumption and death rates in ICU patients who were divided into three groups based on their skeletal muscle area and density as measured by computerized tomography (CT): normal skeletal muscle area, low skeletal muscle area, and combined low skeletal muscle area and density. They discovered that a high protein consumption was related with a decreased 60-day death rate among people with either low skeletal muscle area or both low area and density. However, there was no link established between protein consumption and long-term difficulties in those with normal skeletal muscle area.

In our study, we found that thigh musle thickness was higher among those with higher protein intake compared to those with lower ones at day 7 (6.7 ± 0.3 vs 5.9 ± 0.1). However, this difference was slightly apparent on day 3 on which thigh musle thickness was 5.8 ± 0.3 vs 5.4 ±0.2. Our results matches what was reported by Ferrie et al., [19] who found that the thigh musle thickness was more among high protein intake group compared to the other one (6.8±2.1 vs 5.8±1.9). There was a debate concerning the time to start the parenteral nutrition. Despite there is decrease of evidence concerning the parenteral nutrition start, it is agreed that patients should start their enteral nutrition as soon as possible. Also, the parenteral nutrition needed to be supplemented early to avoid the complications of malnutrition [20].

In our study patients started parenteral nutrition after a median duration of 22 (11.75 – 28.25) hours for high protein intake group vs 24 (15 – 31) hours respectively. This was slightly later than what was reported by Ferrie et al., who reported that patients in their study started the parenteral nutrition after a median duration of 17 (7.7 – 24) hours for high protein intake group vs 17.5 (10 – 37.5) hours respectively [19].
In our study, we found that the SOFA score was not significantly associated with the amount of protein intake among both groups (p=0.511). This was consistent with Dresen et al., [21] findings who randomly assigned 42 patients with critical illness into 2 groups; low and high protein groups. They found that at the end of the study period, no significant difference was recorded concerning SOFA score between the two groups. On the other hand, the Acute physiology and chronic health evaluation score 2 (APACHE scoring system) is also a good prognostic factor for evaluating the prognosis of ICU patients. It is used as an early predictive tool for patients ‘mortality [22].

In our study we found that APACHEII score was higher among patients with higher protein intake when compared to patients with low

protein intake (22.6 ± 5.9 vs 21.8 ± 4.9) however, this was statistically insignificant (P=0.431). Our results were in concordance with Ferrie et al., who studied 119 patients recently admitted to ICU and found no significant difference was recorded among patients in the 2 groups despite being slightly high among high protein intake group compared to others (25.5 ± 9.4 vs 23.7 ± 8.1) respectively [19]. Also, our results were also similar to Koekkoek et al., [17] who followed up 455 patients admitted to ICU and needed mechanical ventilation. They found that median APACHEII scores were comparable between both groups (23 (18 – 28.5) vs 24 (19 – 29)). This was also statistically insignificant (P=0.167).

Recommendation

In the future, we advocate repeating the study with a bigger sample size and longer follow-up periods.

Conclusion

A critical sickness is a potentially fatal disorder that changes muscle metabolism. This is also linked to muscle protein loss, which raises the protein needs for such individuals in order to enhance their prognosis. For those patients, starting parenteral feeding is critical. High protein consumption was not related with fewer ventilator days, ICU duration of stay, or overall mortality. The APACHE and SOFA scores were not affected by the amount of protein supplied in the form of TPN. Patients with a high protein intake, on the other hand, had greater hand grip strength at the conclusion of the first week of follow-up. Furthermore, increasing protein consumption enhanced quadriceps muscle thickness substantially.

Source of funding: This project was locally funded from El-Minia University.

Conflict of interest: None.

Acknowledgments: We acknowledge all participants included in this investigation.

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