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Original Research Article

Combined Effects of High-Protein Intake and Early Exercise in Adult Intensive Care Patients: A Prospective Study

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Abstract: Critical illness is characterized by substantial hormone- and cytokine-mediated protein metabolism changes in various organs, leading to increased breakdown and decreased synthesis rates. Consequently, a considerable and life-threatening loss of muscle mass occurs. Medical therapeutic measures such as long-term sedation and mechanical ventilation during ICU stay can further enhance this muscle degradation (up to 2 % muscle mass per day leading to clinically relevant symptoms known as ICU-acquired weakness, a clinical symptom that is classified as a secondary disorder. If left unabated, these circumstances might strongly affect long-term patient outcomes. This study consists of 20 mechanically ventilated patients expected to stay in the intensive care unit (ICU) for at least 4 days. We used indirect calorimetry to determine energy expenditure and guide caloric provision to the patients randomized to the high protein and early exercise (HPE) group and the control group. Protein intakes were 1.48 g/kg/day and 1.19 g/kg/day medians respectively; while the former was submitted to two daily sessions of exercise, the latter received routine physiotherapy. We evaluated the primary outcome physical component summary (PCS) score at 3 and 6 months and the secondary outcomes (handgrip strength at ICU discharge and ICU and hospital mortality. In this prospective randomized controlled trial, we found that a high protein intake and resistance training led to an improvement in the physical quality of life of critically ill patients as measured by the PCS score after 3 and 6 months. We also found a reduction in mortality rate and a tendency to improvement in the ICU-acquired weakness measured through handgrip strength in the study group.

Keywords: High-Protein Intake, Early Exercise, Adult Intensive Care Patients.

INTRODUCTION

Critical illness is characterized by substantial hormone- and cytokine-mediated protein metabolism changes in various organs, leading to increased breakdown and decreased synthesis rates. Consequently, a considerable and life-threatening loss of muscle mass occurs. Medical therapeutic measures such as long-term sedation and mechanical ventilation during ICU stay can further enhance this muscle degradation (up to 2 % muscle mass per day leading to clinically relevant symptoms known as ICU-acquired weakness, a clinical symptom that is classified as a secondary disorder. If left unabated, these circumstances might strongly affect long-term patient outcomes. Besides targeted medication and exercise, a quantitatively higher protein intake (compared to actual recommendations for healthy adults) in critically ill patients might be reasonable to cover disease-specific increases in nitrogen/amino acid requirements and, thereby, contribute to overcome marked loss of functional proteins. Besides treatment for the underlying disease or insult, providing adequate nutritional support, according to current guidelines, is vital to counteract muscle wasting and loss of functional capacity associated with a critical illness. Due to its reduction of infectious complications, shorter ICU, and hospital stay, the enteral route is prioritized over parenteral nutrition. Appropriate timing of nutritional support containing the required amounts of energy and protein in intensive care unit (ICU) patients has received considerable attention, in particular during the acute phase of critical illness [1, 2].

Based on observational studies, the European Society for Clinical Nutrition and Metabolism (ESPEN) strongly recommends a daily intake of 1.3 g protein equivalents/kg body weight [BW], while the US-American guidelines even suggest considerably higher protein quantities (1.2–2.0 g/kg BW/d) . Probably due to the broad variations in the study designs (e.g., different patient populations, lack of individualized nutrition concepts including adequate energy supply, different routes of administration), the few RCTs evaluating the effects of higher (> 1.2 g/kg BW/d) protein/amino acid administration on patient outcome (morbidity, mortality, length of stay) and selected metabolic markers (e.g., nitrogen balance; urinary urea, creatinine, and amino acids; glomerular filtration rate, GFR) report inconclusive results. A recent review of RCTs published between 1966 and 2015 comparing different nutritional support strategies in ICU with significant differences in protein delivery could not find any effect on mortality rates. Thus, the final recommendations for an adequate protein supply during critical illness cannot be made. One of the unsolved problems for a reliable definition of protein goals is the optimal intake timing to reach predefined therapeutic goals. While few studies have indicated that protein provision higher than 1.0 g/kg BW/d in the early phase of critical illness seems to be associated with reduced mortality, other investigations have shown that early high-protein administration (> 1.2 g/kg BW/d) might worsen instead of improving the patient outcome, especially during hyperenergetic nutrition therapy [3].

Generally, it is well known that patients in the acute phase (ebb phase) of the stress response are less capable of utilizing nutrients, thereby implying that early high-dose protein administration might not be beneficial. In the later phase (flow phase) of metabolic stress, insulin sensitivity gradually improves, and the human bodys' capability to metabolize exogenous substrates increases accordingly. Consequently, it could be hypothesized that high-protein medical nutrition after the onset of trauma might effectively reduce endogenous proteolysis, which could contribute to muscle mass preservation [4].

OBJECTIVE

To study combined effects of high-protein intake and early exercise in adult intensive care patients.

METHODOLOGY

This study consists of 20 mechanically ventilated patients expected to stay in the intensive care unit (ICU) for at least 4 days. We used indirect calorimetry to determine energy expenditure and guide caloric provision to the patients randomized to the high protein and early exercise (HPE) group and the control group. Protein intakes were 1.48 g/kg/day and 1.19 g/kg/day medians respectively; while the former was submitted to two daily sessions of exercise, the latter received routine physiotherapy. We evaluated the primary outcome physical component summary (PCS) score at 3 and 6 months and the secondary outcomes (handgrip strength at ICU discharge and ICU and hospital mortality.

RESULTS

In this trial of mechanically ventilated patients admitted to the ICU for at least 4 days, we found a significant improvement in the PCS score assessed at 3 and 6 months in the patients of the HPE group. We also found a significant reduction in mortality in the HPE group. The multivariate analysis showed an independent association between lower age and a better 3-month PCS and that between a better 6-month PCS and lower age, lower nutrition risk, and belonging to the HPE group. In the HPE group, we observed a borderline improvement in the acquired weakness evaluated through handgrip strength at the time of ICU discharge or after 21 days of ICU stay. To the best of our knowledge, this is the first study to demonstrate that a high protein intake coupled with early resistance training improves the physical component of quality of life and, more importantly, the mortality in critically ill patients.

DISCUSSION

An association between higher protein intake and lower mortality was demonstrated in several observational studies in a heterogeneous ICU population. Few studies specifically report early protein intake. In a retrospective cohort study, Bendavid *et al*., found an association between a protein intake of >0.7 g/kg/d during the first 3 days of ICU admission and lower 60-day all-cause mortality. Additionally, in another large retrospective cohort study, Zusman *et al*., also found a significant association between day 3 protein intake of 1 g/kg/d and lower mortality. However, higher protein delivery in the first week was found to be associated with greater muscle wasting in a small selected cohort of patients with prolonged critical illness. Additionally, Koekkoek *et al*., found lower mortality when protein intake was gradually increased during 7 days. Similarly, a post-hoc analysis of the EPANIC trial suggested that the day 3 protein/amino acid dose, rather than the glucose dose, explained the delayed recovery in the early PN group.

An enteral formula with an HP:E ratio containing 33% whey protein hydrolysate as a protein source appears to be suitable for early enteral feeding of critically ill patients requiring mechanical ventilation. However, larger and randomized trials are needed in order to recommend its use as a standard of care in the ICU. Due to the good GI tolerance, individual protein targets in line with current recommendations (≥1.3 g/kgBW/d) could be met within 72 h after initiation of enteral feeding with the HPE formula, while, over the same period of time, energy provision was virtually met, but did not exceed a moderate caloric target of 20 kcal/kgBW/d.

Allingstrup *et al*., analyzed 199 patients randomized to receive a caloric intake determined by indirect calorimetry; they also received a higher protein intake than a group receiving the usual protein intake and 25 kcal/kg/day. The study found no difference in the PCS score for quality of life between the two groups, when assessed 6 months after randomization. There are significant differences between our study and that of Allingstrup *et al*., In that study, urinary urea was used to determine the protein supply in the study group, but the patients received 1.5 g / kg of protein from the first day as well as the energy supply was 100% of what was measured by calorimetry [1-3].

Ferrie *et al*., randomized ICU patients to receive parenteral nutrition at 1.2 g / kg / day of protein, when compared with 0.8 g / kg / day; the authors did find differences in short-term outcomes but no difference in long-term outcomes [4].

In a cohort of 726 non-septic ICU patients, Weijs *et al*., found that the mortality declined with a high protein intake but increased with energy overfeeding [5].

Nicolo *et al*., analyzed 2824 critically ill patients who remained in the ICU for at least 4 days; the study evaluated the impact of protein delivery on mortality and observed that the administration of the goal protein higher than that of 80% led to a 40% reduction in mortality. Conversely, an increase in energy delivery was not associated with a reduction in mortality [6].

Looijaard *et al*., in a recent study, evaluated patients with a low skeletal muscle area and density on admission; the findings revealed that early protein intake ≥1.2 g/kg/d was associated with a lower mortality in patients with a low skeletal muscle area and density [7].

CONCLUSION

In this prospective randomized controlled trial, we found that a high protein intake and resistance training led to an improvement in the physical quality of life of critically ill patients as measured by the PCS score after 3 and 6 months. We also found a reduction in mortality rate and a tendency to improvement in in the ICU-acquired weakness measured through handgrip strength in the study group.

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