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High-protein hypocaloric vs normocaloric enteral nutrition in critically ill patients: A randomized clinical trial

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ABSTRACT

Purpose: Appropriate caloric intake in critically ill patients receiving enteral nutrition is controversial. This study evaluates the impact of different caloric regimens on severity of organ failure measured with Sequential Organ Failure Assessment (SOFA).
Materials and methods: We conducted a randomized prospective controlled trial. Study population included adult intensive care unit (ICU) patients expected to require enteral nutrition for more than 96 hours. Goals in the intervention group were hypocaloric (15 kcal/kg per day) enteral nutrition compared to normocaloric (25 kcal/kg per day) enteral nutrition, both with hyperproteic intake (1.7 g of protein/kg per day). Primary end point was change in SOFA score (ΔSOFA) from baseline at 48 hours. Secondary end points were ΔSOFA at 96 hours, insulin requirements, hyperglycemia or hypoglycemic episodes, length of ICU stay, days on ventilator, and 28-day mortality.
Results: After screening 443 patients, 120 patients were analyzed. There were no differences between groups in baseline characteristics. We did not find a statistically significant difference in ΔSOFA at 48 hours. Patients in the hypocaloric group showed lower average daily insulin requirements and percentage of patients requiring any insulin.
Conclusions: Hyperproteic, hypocaloric nutrition did not show different outcomes compared to normocaloric nutrition, except lower insulin requirements. Hypocaloric nutrition could provide a more physiologic approach with lower need for care and metabolic impact.

1. Introduction

Daily energy requirements may vary from 1200 kcal during rest to 14 000 kcal in individuals undergoing high-performance activities [1,2]. In critically ill patients receiving enteral nutrition (EN), the question of what is the appropriate caloric intake is still unanswered. Current guidelines recommend EN over parenteral nutrition because of its lower risk of infectious complications, fistulas, and bacterial translocation, reducing length of stay [3–6]. Several studies suggest that EN is the preferred choice in most intensive care unit (ICU) patients [7–12] and should be initiated within the first 24 to 48 hours [5,6]. However, there is no consensus on the optimal caloric requirement in critically ill patients using EN. Different predictive equations are commonly used [13,14].

A recent clinical trial performed by our research group compared hypocaloric EN (12 kcal/kg per day) with a protein intake of 1.4 g/kg per day, with a normocaloric scheme defined as 25 kcal/kg per day and 20% protein. However, for several reasons, the latter group ended up receiving only 14 kcal/kg per day, with a protein intake of 0.76 g/kg per day. As such, groups received similar caloric intake and only differed in protein intake. The former (hyperproteic) group showed better outcomes in terms of Sequential Organ Failure Assessment (SOFA) score progress, lower blood sugar levels, and a tendency to decrease days on mechanical ventilation and ICU length of stay [15].

Therefore, we believe that, to evaluate the optimal caloric intake in critically ill patients, it is necessary to compare 2 regimes with high protein intake, but with different energy supply. A trial comparing a normocaloric high-protein scheme (25 kcal/kg per day) and a hypocaloric high-protein scheme known as a controlled starvation (low doses of carbohydrates and high-protein intake) [16] would allow physicians to choose a caloric scheme, given a protein intake between 1.5 and 2 g/kg per day in catabolic patients [15,17–20]. Low

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caloric and high-protein nutrition has proven better in critically ill obese patient [21], but there are no studies with this regimen in nonobese patients.

This randomized double-blind controlled trial compared 2 caloric schemes (15 or 25 kcal/kg per day) in a high-protein scheme (1.7 g/kg per day) in critically ill patients.

2. Methods

2.1. Study population

This randomized parallel arm clinical study was performed at the 30-bed ICU of our tertiary level university hospital. We enrolled newly admitted patients, which mostly came directly from the emergency unit. Patients were recruited during the 20-month period December 2013 to July 2015. Study population consisted of adult patients (18 years or older) admitted in the ICU and expected to require EN through nasoenteric tube for at least 96 hours. We excluded patients receiving previous nutritional support in the same hospitalization, with concomitant parenteral nutrition, pregnant women, in transplantation program, chronic renal failure, uremic encephalopathy, diabetes, morbid obesity, or do-not-resuscitate orders.

2.2. Randomization and blinding

Randomization was performed using dark sealed envelopes with computer-generated random allocations. Analysis only considered patients who completed 96 hours of follow-up and received more than 5 kcal/kg per day. When patients were excluded, their envelopes were returned to the sequence for patient replacement, until the calculated sample size was accomplished. All analyzed patients were assessed until death during the hospitalization or 28 days after their enrollment through telephone interview if discharged earlier. One investigator (LGV) knew patient allocation and prescribed and supervised the administration of nutritional regimens after randomization. Patients and ICU staff deciding on the rest of medical care were blinded to patient allocation; nutritional information and regimen formulation were not registered in clinical records, except for general information such as total liquids administered.

2.3. Intervention

Patients were allocated to 1 of 2 groups. Ideal body weight was used to calculate caloric and protein requirements. Nutritional goals in the intervention group were a hypocaloric EN of 15 kcal/kg per day of total calories and high protein intake (1.7 g of protein/kg per day). Control group goals were a normocaloric EN of 25 kcal/kg per day with high protein intake (1.7 g of protein/kg per day). Definitions of hyperproteic and normocaloric nutrition are taken from the American Society for Parenteral and Enteral Nutrition guidelines [5], and hypocaloric nutrition represented 60% of that. A commercial enteral formula was adjusted to achieve caloric goals (Online Table 1) and was enriched with additional modules of whey and soy protein diluted in water, given in 3 or 4 daily boluses (Online Table 2). All patients received allocated nutritional regimen until day 7. If further EN was necessary, all patients received normocaloric nutrition.

2.4. End points

Blinded ICU personnel reported clinical events and laboratory values in clinical records. One investigator (LGV) used these data to calculate SOFA score and report outcomes. Primary end point of the study was change in SOFA score from baseline (ΔSOFA) at 48 hours. Secondary end points were ΔSOFA at 96 hours, insulin requirements (mean daily units of insulin), frequency of hyperglycemia episodes (glycemic measurements >180 mg/dL) or hypoglycemia episodes (glycemic measurements <45 mg/dL), length of ICU stay, days on ventilator, days to start nutrition, and mortality within 28 days of randomization. An adverse event in our clinical trial was defined as an unfavorable and unexpected change in health or laboratory findings in trial participants. We had 3 categories: mild (tolerable transitory event), moderate (an uncomfortable event that disrupted normal activities), and severe (a life-threatening event). *Feeding intolerance* was defined as any of these 3 symptoms: vomiting defined as an ejection of stomach contents through the mouth (>2 episodes in 24 h), diarrhea defined as liquid stool that changes in amount (>3 episodes in 24 hours), and bowel distension defined by clinical examination and lasting at least 24 hours.

2.5. Statistical analysis

Sample size was calculated using TAMAMU software (Pontificia Universidad Javeriana, Bogota, Colombia). Sixty patients per arm were necessary to provide 80% power and α error of .05 to detect a 15% (1.7 points) difference in ΔSOFA at 48 hours between the 2 groups with an SD of 1.9 with a 2-tailed *t* test.

We used R version 3.2.2 (The R Foundation for Statistical Computing, 2015) for statistical analysis. Baseline characteristics and outcomes were analyzed depending on the nature of the variables. Normality of quantitative data was assessed by inspecting histograms and quantile-quantile plots. Normally distributed data were analyzed with a 2-tailed *t* test ($P = .05$). Otherwise, Wilcoxon rank sum test was used. We assessed categorical data using a normal *z* test. Contingency tables greater than 2×2 in size were analyzed with χ^2 or Fisher exact test when sparse data (<5 observations) were present. We performed a multivariate linear regression analysis for the primary outcome to check for possible confounding factors as antibiotic use, dialysis, blood cell or platelet transfusions, and cardiopulmonary resuscitation.

2.6. Ethical considerations

Written informed consent before enrollment in the study was provided by relatives. The study was approved by the Ethics Committee of the Pontificia Universidad Javeriana and complied with the provisions of the Good Clinical Practice Guidelines, the Declaration of Helsinki, and local regulations. This trial has been registered in ClinicalTrials.gov, identifier NCT02577211.

2.7. Role of the funding source

The study sponsor provided an unrestricted grant and was not involved in any of the stages of the study. All authors had full access to the data, and the corresponding author had final responsibility to submit the manuscript for publication.

3. Results

We assessed 443 patients and found 187 eligible patients who were then randomized. Exclusions after randomization happened in 36 hypocaloric and 31 normocaloric patients. Reasons for exclusion were balanced in both intervention groups. Calculated sample size was achieved (Fig. 1).

Baseline characteristics were similar between study groups (Table 1). Respiratory and neurologic etiologies were the main causes of ICU admission in both groups. Most patients had a B or C baseline subjective global assessment nutritional status. Intervention characteristics showed the expected differences. The delay between ICU admission and start of the EN was similar. The hypocaloric intake group received a minor amount of total calories, total formula, and metabolic flux and more protein modules compared to the normocaloric group. Protein intake was similar (Table 2). This tendency was stable during the 96 hours of observation in the ICU (Fig. 2).