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HIGH PROTEIN PARENTERAL NUTRITION COMPENDIUM OF STUDIES 2019

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INTRODUCTION

This compendium includes summaries of ten key studies supporting the use of high protein parenteral nutrition (PN) in critically ill patients.

IN CRITICALLY ILL PATIENTS, HIGH PROTEIN INTAKE MATTERS

Protein, not calories, is the crucial macronutrient in catabolic critical illness.[1] However, most critically ill patients receive half the recommended protein in ICU patients during their first week in the ICU.[1]

Compared with standard intake, higher protein in ICU patients as prescribed by ASPEN[2] and ESPEN[3] guidelines was associated with patient-focused improvements in ICU patients,[4] fewer ventilator days[5] and lower mortality rates.[5-9]

	PROTEIN INTAKE	ADDITIONAL GUIDANCE
A.S.P.E.N.[2]	1.2-2.0 g/kg IBW/day	If BMI < 30 kg/ m²
	≥ 2 g/kg IBW/day	If BMI 30-40 kg/m²
	≥ 2.5 g/kg IBW/day	If BMI ≥ 40 kg/m²
ESPEN[3]	1.3 g/kg	Delivered progressively

Protein requirements may be higher in burn or multitrauma patients[2]

BMI - body mass index
IBW - ideal body weight

References: 1. Hoffer LJ, et al. F1000 Research 2016;5:2531. 2. McClave SA, et al. JPEN J Parenter Enteral Nutr Feb. 2016;40:159-211. 3. Singer P, et al., Clin Nutr 2018, https://doi.org/10.1016/j.clnu.2018.08.037 4. Ferrie S, et al. JPEN J Parenter Enteral Nutr 2016;40:795-805. 5. Elke G, et al. Crit Care 2014;18:R29. 6. Nicolo M, et al. JPEN J Parenter Enteral Nutr 2016;40:45-51. 7. Alberda C, et al. Intensive Care Med 2009;35:1728-37. 8. Allingstrup MJ, et al. Clin Nutr 2012;31:462-8. 9. Weijs PJ, et al. Crit Care 2014;17:183-9.

HIGHLIGHTED STUDIES

The Relationship Between Nutritional Intake and Clinical Outcomes in Critically Ill Patients: Results of an International Multicenter Observational Study

Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day A, Dhaliwal R, Heyland D. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. *Intensive Care Medicine*. 2009 July; 35:1728-1737.

LINK ▶

BACKGROUND

Prior research demonstrates that a non-critically ill patient's pre-morbid nutritional status may impact their response to nutritional intervention. These patients may enter the hospital with limited nutritional reserves from being underfed, which causes them to become critically malnourished faster than other patients. However, the optimal amount of energy and protein for critically ill patients to reduce morbidity and mortality remains controversial. Some observational studies link critically ill patients' cumulative energy deficit with negative clinical outcomes. Yet, another observational study by Kirshnan et al.,[1] found that patients who received 33% and 66% of their estimated energy needs had better clinical outcomes than patients who were closer to 100% of calorie goals.

OBJECTIVE

The purpose of the study was to explore the relationship between the amount of energy and protein given to patients and their clinical outcomes, such as 60-day mortality and ventilator-free days (VFD), and how their pre-morbid nutritional status impacted this relationship.

METHODS

Nutrition practices in 167 intensive care units across 37 countries were examined in an observational cohort study. Eligible ICUs needed to have an employee well-versed in clinical nutrition with the resources to collect the required patient data within the study period. ICU patients who were older than 18, mechanically ventilated within the first 48 hours of admission and who remained in the ICU for more than 72 hours were included. Patients' demographics were collected from a secure Web-based data collection tool, and their type and amount of nutrition received were recorded daily for a maximum of 12 days. Their 60-day mortality and VFDs were also recorded prospectively.

Body mass index (BMI, kg/m2) was also used as a marker of nutritional status prior to ICU admission. BMI levels were set at <20, 20 to <25, 25 to <30, 30 to <35, 35 to <40, and ≥40 kg/m2. Logistic regression models, with random ICU intercepts and prior known risk factors for mortality, evaluated the relationship between nutrition and 60-day mortality and VFDs, plus BMI impact on this relationship. The models predicted 60-day mortality by the daily average of total energy and protein received during the first 12 ICU days prior to death or permanent move to exclusive oral feeding.

Reference: 1. Krishnan JA, et al. Chest 2003;124:297-305.

RESULTS

Data was collected on 2,772 mechanically ventilated patients who received an average of 1,034 kcal/day and 47g protein/day. In the study group, 69% of patients received enteral nutrition (EN) only, 8% parenteral nutrition (PN) only, 17.6% EN plus PN and 5.4% no EN or PN. Overall, patients consumed 59.2% of the energy and 56% of protein prescribed, with patients in the BMI <20 group receiving greater amounts than patients with higher BMIs.

ICU patients who received an additional 1,000 calories per day had reduced mortality [odds ratio for 60-day mortality 0.76; 95% confidence intervals (CI) 0.61-0.95, p = 0.014] and an increased number of VFDs (3.5 VFD, 95% CI 1.2-5.9, p = 0.003). An additional 30 grams of protein per day was associated with a reduction in mortality (an adjusted OR 0.84 (95% CI: 0.74-0.96, p=0.008)), but a similar relationship was not seen for VFDs. The impact of increased calories on lower mortality was seen in patients with a BMI <25 and ≥35, but not for patients with a BMI 25 to <35.

CONCLUSIONS

Increased intakes of energy and protein appear to be associated with improved clinical outcomes in critically ill patients, particularly when BMI is <25 or ≥35.

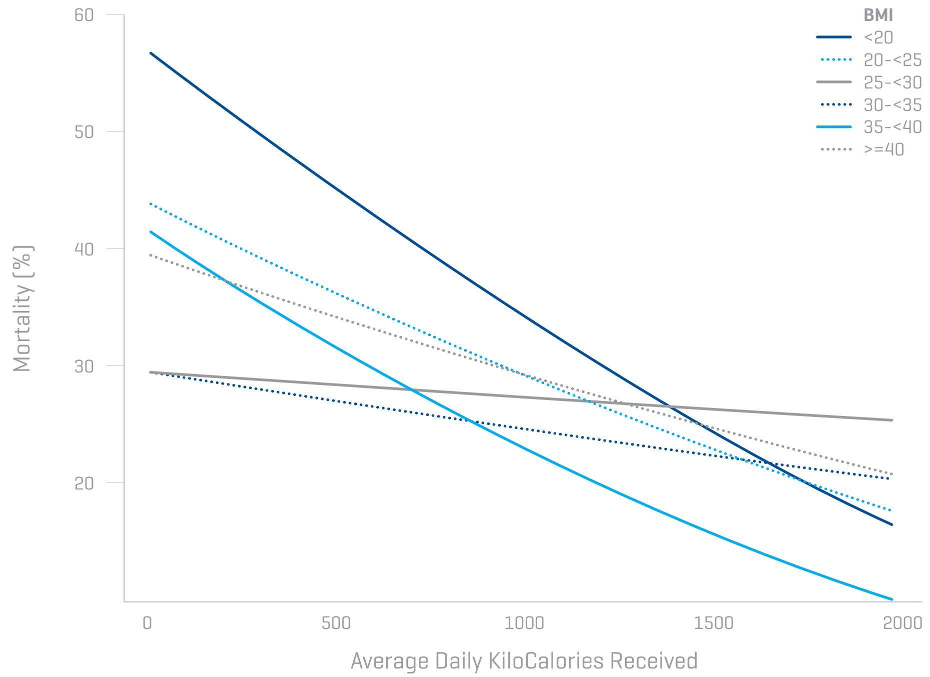


Figure 1 The relationship between increasing calories/day and 60-day mortality by BMI.
BMI body mass index

Provision of Protein and Energy in Relation to Measured Requirements in Intensive Care Patients

Allingstrup MJ, Esmailzadeh N, Wilkens Knudsen A, Espersen K, Hartvig Jensen T, Wiis J, Perner A, Kondrup J. Provision of protein and energy in relation to measured requirements in intensive care patients. *Clinical Nutrition.* 2012; 31:462-8.

LINK ▶

BACKGROUND

Adequate nutrition is important for intensive care patients; however, confirming that higher protein improves outcomes still requires further study. In 2010, a review of observational studies on ICU nutrition encouraged proper nutritional support, as the studies indicated undernourished patients had higher rates of complications, longer stays in the hospital and increased costs. Further, ICU patients' survival time improved when given adequate energy and protein (about 25 kcal/kg/day, determined by indirect calorimetry, and 1.2 g protein/kg/day), according to an observational ICU study. It is not known if the link between protein and survival was due to maintenance of nitrogen balance and lean body mass (LBM) as nitrogen balance was not measured in the study. In another observational study, an inadequate provision of energy and protein in ICU patients during their first week was related to higher mortality rates.

OBJECTIVE

The aim of this study was to determine if patient mortality was related to intake of energy and protein and amino acids (AA), or nitrogen (N) or energy balances, and if early events during ICU admission (such as death, discharge or complications) were caused by these relationships.

METHODS

Two groups of 113 patients, consecutively selected, mixed medical-surgical patients, were studied in an observational cohort study at a tertiary referral hospital. The patients in the first group were recruited between January 2006 and May 2006, and the second group was recruited from November 2009 to May 2010. Patients were selected whose energy and protein requirements were uncertain, such as those who were on a ventilator and had a burn injury >15% body surface area or severe sepsis (i.e., documented/suspected infection + two SIRS criteria + acute organ dysfunction, hypoperfusion or hypotension).

The initial energy and protein targets were 25-30 kcal/kg/day and 1.2-1.5 g/kg/day until indirect calorimetry and 24-hour urea excretion were available. Within 24 hours of admission, patients were administered enteral nutrition, which was supplemented with parenteral nutrition such as amino acids and glucose 50% at the doctors' discretion, if needed. The patients were also divided into three groups based on the amount of protein they received: low protein and AA (0.79 ± 0.29 g/kg/day), medium protein and AA (1.06 ± 0.23 g/kg/day), and high protein and AA (1.46 ± 0.29 g/kg/day), P = <0.001. The staff caring for the patients were made aware of the results, but investigators did not interfere with the prescribed amount of nutrition. All patients' variables were followed until death or discharge, and length of stay was recorded.

RESULTS

ICU patients who received the lowest provision of protein and amino acids died earlier than other patients. Mortality was not affected by the provision of energy, measured resting energy expenditure or energy and nitrogen balance. A Cox regression analysis confirmed that increased protein provision (even when adjusted for baseline prognostic variables) lead to a significantly decreased hazard ratio of death. During the two study periods, 25 patients died in the ICU (23%), and their energy and protein balances had considerable deficits. Survival was not significantly related to gender, co-morbidity or the two periods of investigation. The intake of protein and survival rates were related even when adjusted for Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores or age. Twenty-four deaths did occur among the 100 patients with severe sepsis. Early non-infectious complications (<6 days) versus late complications showed a hazard ratio of 5.43 (95%CI: 1.12-26.4), P = 0.03, analyzed together with provision of protein and amino acids. Results suggest that the increase in survival goes up with the increasing intervals of protein & AA provision from low to medium to high—0.79, 1.06 and 1.46 g protein g/kg/day correlated with a 10-day survival rate of 50%, 78% and 87%, respectively.

CONCLUSIONS

Death occurred earlier in the tertile of patients with the lowest provision of protein and amino acids. The most plausible interpretation of these data is that this group developed non-infectious complications more rapidly and that this more often was related to an unfavourable outcome because of the inadequate nutritional support. Provision of energy, measured resting energy expenditure, or energy and N balances was not related to hazard of mortality in these ICU patients. Based on these data, a randomised trial of the provision of 1.5 g/kg/day of protein/amino acids in ICU patients seems worthwhile.

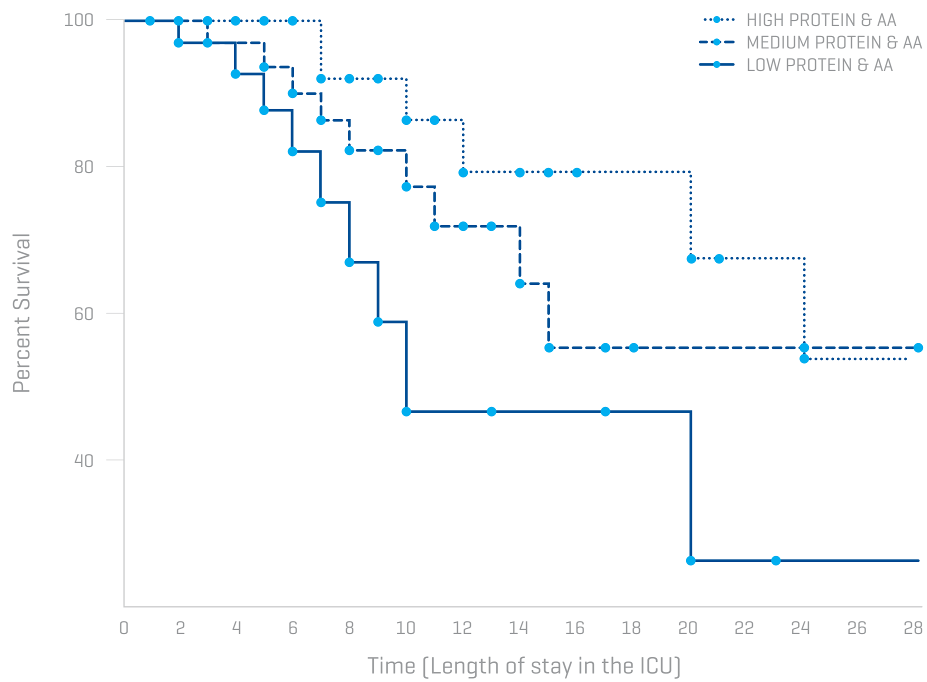


Figure 1 28-Day survival in the ICU. KaplaneMeier curve that depicts 28-day survival in three groups of patients, ranked according to decreasing provision of protein during their intensive care unit stay. Initial number of patients in the three groups: Low protein&AA: 37; medium protein&AA: 38; High protein&AA: 38. The average provision of protein in the three groups were: low protein&AA: 53.8 g/day; medium protein&AA: 84.3; high protein&AA: 114.9 g/day. The square brackets indicate the number of patients remaining at risk on day 10, i.e. neither censored nor dead. The knobs indicate censoring of one or several patients. Eight patients had longer observation time than 28 days, with a maximum of 77 days. Comparison of curves for all patients: Mantel logrank P ¼ 0.021; BresloweGehan: P ¼ 0.027. Log-rank test for trend: P ¼ 0.011.

Intravenous Amino Acid Therapy for Kidney Function in Critically Ill Patients: A Randomized Controlled Trial

Doig G, Simpson F, Bellomo R, Heighes P, Sweetman E, Chesher D, Pollock C, Davies A, Botha J, Harrigan P, Reade M. Intravenous amino acid therapy for kidney function in critically ill patients: A randomized controlled trial. *Intensive Care Medicine.* 2015 April; 41:1197–1208.

LINK ▶

BACKGROUND

Critically ill patients who develop acute kidney injury (AKI), characterized by severe loss of glomerular filtration rate (GFR), are more likely to have a longer intensive care unit (ICU) stay and an increased risk of death. However, no interventions exist to prevent AKI or preserve GFR for these patients.

If patients with chronic kidney disease (CKD) consume a high-protein diet over a prolonged period of time, it is accepted they will quickly progress to advanced stages of CKD. Animal models, though, have shown that kidneys can be protected from acute ischemic insults by an increase in renal blood flow in response to a short-term amino acid infusion. In 1973, a clinical trial of 53 critically ill patients also reported that a short-term infusion of amino acids helped patients recover faster from severe acute renal failure. A 14-patient clinical trial published in 2007 demonstrated that critically ill patients with a creatinine clearance below 50 mL/min who randomly received a short-term higher dose of amino acids in their IV were more likely to preserve diuresis and less furosemide to reach a negative fluid balance. Also, a randomized controlled trial (RCT) of 242 patients at high risk of renal dysfunction reported patients randomized to receive higher daily protein intake were significantly less likely to require renal replacement therapy (RRT).

OBJECTIVE

This study examined whether kidney function in critically ill patients could be preserved through short-term daily amino acid therapy by intravenous (IV) supplementation with standard amino acids.

METHODS

From December 2010 to February 2013, this multi-center, phase II, randomized clinical trial was conducted in the ICUs of 16 community and tertiary hospitals in Australia and New Zealand. Critically ill patients who had a high risk of renal dysfunction and body mass index (BMI) greater than 18 kg/m2 and were expected to remain in the ICU for more than two days participated in the study. They were randomized to receive a daily supplement of up to 100 g of IV amino acids or standard care (a continuous infusion of a standard mixture of 100 g/L of L-amino acids from Synthamin 17 Electrolyte Free, Baxter Healthcare, Australia), which was maintained by a central randomization Web server. The amino acid infusion totaled 2.0 g/kg/day after adjusting for a patient's ideal body weight and protein intake from standard nutrition sources, and was continued until ICU discharge. The study intervention was not blind.

The patients' duration of renal dysfunction, adjusted for time at risk in the ICU, was the primary outcome. Secondary outcomes were additional measures of renal function, such as use of RRT and eGFR estimated from serum creatinine and eGFR from serum cystatin C. Tertiary outcomes included vital status at study day 90, Zubrod/WHO Performance Status and other in-hospital care measures such as ICU stay, hospital stay, mechanical ventilation days and organ dysfunctions.

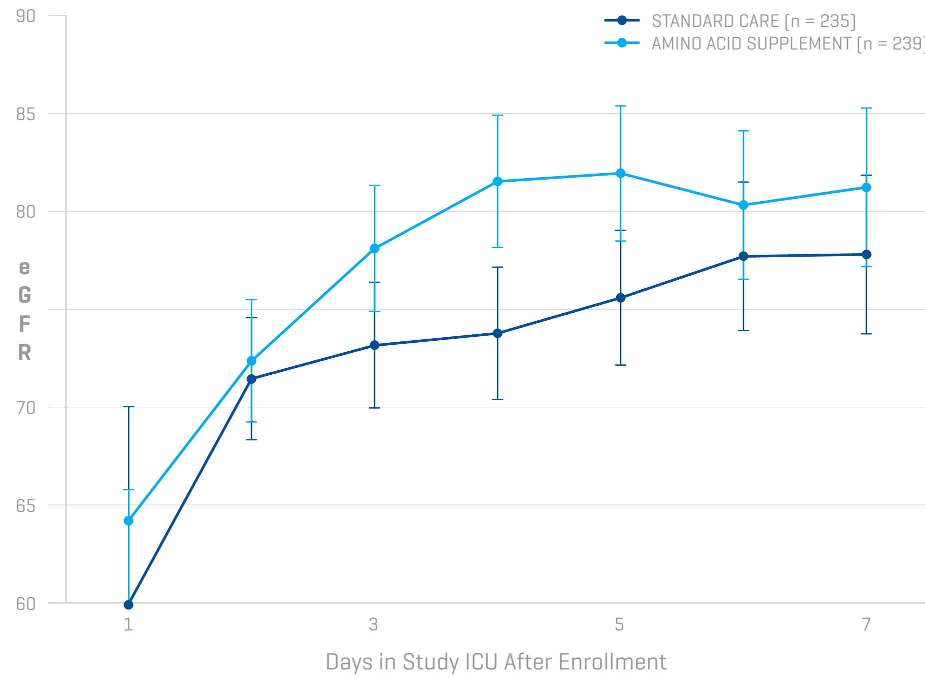
RESULTS

The study enrolled and randomized 474 patients (235 to standard care and 239 to IV amino acid therapy). The patients who received amino acid therapy at enrollment had higher APACHE II scores (20.2 ± 6.8 vs. 21.7 ± 7.6, P = 0.02), and more of the patients already had pre-existing renal dysfunction (29/235 vs. 44/239, P = 0.07). After study enrollment, the length of renal dysfunction was the same between groups (mean difference 0.21 AKI days per 10 patient ICU days, 95 % CI -0.27 to 1.04, P = 0.45). However, amino acid therapy did significantly improve eGFR (treatment group x time interaction, P = 0.004) with an early peak difference of 7.7 mL/min/1.73 m^2 (95 % CI 1.0–14.5 mL/min/1.73 m^2, P = 0.02) on study day four. Also, daily urine output was significantly increased (+300 mL/day, 95 % CI 145-455 mL, P = 0.0002).

CONCLUSIONS

A daily IV supplement of standard amino acids did not affect the study's primary outcome, duration of renal dysfunction. However, the study intervention did improve eGFR and increased urine output. These physiological effects suggest the existence of renal functional reserve in critical illness and justify further investigations of this treatment in targeted high-risk populations.

Estimated Glomerular Filtration Rate (CKD-EPI), Post-randomization 474 Critically Ill Patients



Standard Care	n = 234	220	198	170	148	133	120
Amino Acid Supplement	n = 238	231	210	182	160	141	124

Patients in ICU at end of each study day

Figure 1 Estimated glomerular filtration rate (CKDEPIcreatinine) by day, postrandomization. CKDEPIcreatinine was estimated from creatinine using the equations developed by Levey et al. [20]. ICU intensive care unit. P = 0.004 for treatment 9 time interaction from repeated measures ANOVA. Error bars indicate 95 % confidence intervals around differences between groups at each time point

Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition

Ferrie S, Allman-Farinelli M, Daley M, Smith K. Protein Requirements in the critically ill: a randomized controlled trial using parenteral nutrition. *Journal of Parenteral and Enteral Nutrition.* 2016 Aug;40(6):795-805.

LINK ▶

BACKGROUND

Observational studies have largely been used to recommend high protein/amino acid provisions to critically ill patients (1.2–2.0 g/kg/day, compared with 0.8 g/kg/day for healthy people). However, there is currently no randomized study that makes this same comparison.

OBJECTIVE

This study investigated whether an increased dose of amino acids for patients during their first few days in the ICU would lead to better handgrip strength at ICU discharge as a primary outcome, and an improved fatigue score, muscle mass, handgrip strength and/or nitrogen balance as secondary outcomes.

METHODS

Overall, 119 patients (and one patient whose family withdrew consent after she died after 16 hours on the high amino acids solution) received randomized, blinded PN solutions with amino acids at 0.8 g/kg or 1.2 g/kg. They were selected from a general medical/surgical ICU in a large tertiary-referral teaching hospital. The first study group had 60 patients and the second group had 59, during a 12-month period from 2013 to 2014. Patients were disqualified if younger than 16 years, not expected to receive at least 3 days of PN, or had already received significant nutrition recently (>1 L of non-study PN solution or oral/enteral nutrition [EN] providing >30% of estimated requirements in the past 3 days).

The PN solutions utilized were Baxter 3CB containing 6.6 g Nitrogen/L or Baxter 3CB containing 9 g Nitrogen/L, and were given via a central venous access device with vitamins and trace elements for 10 days or until ICU discharge. They were packaged identically by the hospital's independent research pharmacist and labeled with one of four codes. The patients, staff, study investigators and data analysts were blind to the treatment allocation. Each day, total energy and protein intake were calculated and recorded, as well from EN, dextrose solutions or propofol infusions, if administered.

The study's primary outcome was handgrip strength at ICU discharge. Patients were also evaluated on day 7 for secondary outcomes such as handgrip strength, fatigue score, nitrogen balance, arm and leg muscle thickness by ultrasound measures, prealbumin and creatinine. Their ICU and hospital mortality and length of stay were noted, and mortality 6 months after study enrollment.

RESULTS

Handgrip strength at ICU discharge was not significantly different between the two groups (p = .054). The group receiving higher doses of amino acids did demonstrate an improved handgrip strength on day seven, greater muscle thickness on ultrasound and reduced Chalder fatigue score. In addition, their mean (SD) nitrogen balance of -0.5 (3.1) g/d on day three compared favorably to the lower amino acids group -5.6 (1.8) g/d nitrogen balance. By day seven, however, the nitrogen balances were not significantly different. Further, the groups showed no difference in mortality or length-of-stay measures. Patient outcomes were independently affected by their age, APACHE II score, gender and nutrition status.

CONCLUSIONS

ICU patients on PN who received a higher dose of amino acids did show improvements in a number of different outcome measures. This study provides support for current guideline recommendations regarding higher protein in ICU patients.

Optimisation of Energy Provision With Supplemental Parenteral Nutrition in Critically Ill Patients: A Randomised Controlled Clinical Trial

Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C, Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. *Lancet.* 2013;381(9864):385-93.

LINK ▶

BACKGROUND

Nutrition plays a key role in ICU patient recovery. When the gastrointestinal tract is working, guidelines recommend enteral nutrition (EN) or tube feeding. However, oftentimes EN alone cannot provide enough energy or protein, leading to underfeeding. Further, if introduced too soon to stable patients, EN can lead to problems such as gastrointestinal intolerance and bronchoaspiration with an increased risk of pneumonia. Meta-analyses show parental nutrition (PN) or intravenous nutrition, is not associated with increased mortality, but timing is critical. If combined with EN too long, patients can be overfed leading to new problems such as infection and metabolic disturbances, including hyperglycemia and liver dysfunction, which can also result in extended ventilator time.

OBJECTIVE

The purpose of this study was to see if critically ill patients could have improved outcomes if given supplemental parenteral nutrition (SPN), which is a combination of EN and PN when EN is insufficient, to reach 100% of the energy target during the fourth through eighth days in the ICU.

METHODS

The two-center, randomized, controlled, intervention trial, enrolled 305 patients, with 153 patients randomly assigned to SPN and 152 to EN. In the study group, 30 patients did not finish the trial, largely due to protocol violations. Between days four and eight, the mean energy delivery was 28 kcal/kg per day for the SPN group and 20 kcal/kg per day for the EN group.

Eligible patients had received less than 60 percent of their nutrition from EN on their third day in the ICU, were expected to stay in the ICU at least five more days, were predicted to live for more than seven days and had a functioning gastrointestinal tract. Patients were randomly assigned to receive SPN or EN only.

After randomization took place, study patient energy targets were calculated through indirect calorimetry on their third day in the ICU to determine nutrition for day four. When energy target calculation with indirect calorimetry was not possible, energy targets were set at 25 and 30 kcal per kg of ideal bodyweight per day for men and women, respectively. On day four, SPN was administered through central or peripheral catheter for five days. Both the EN and PN formulas came from four different manufacturers. The PN formulas consisted of 0.62–1.37 kcal/mL of energy (20 percent proteins, 29 percent lipids [15 percent medium-chain triglycerides] and 51 percent carbohydrates). Twice a day, patients receiving SPN were evaluated to ensure they reached 100 percent of their energy target.

The primary endpoint was occurrence of a hospital acquired infection (nosocomial) after the testing period, from day nine until day 28. Secondary endpoints were the number of days the patient was on antibiotics, the extent of invasive and non-invasive mechanical ventilation, length of stay in the ICU and hospital, mortality in the ICU, general mortality, glycaemia, drug administration and other factors.

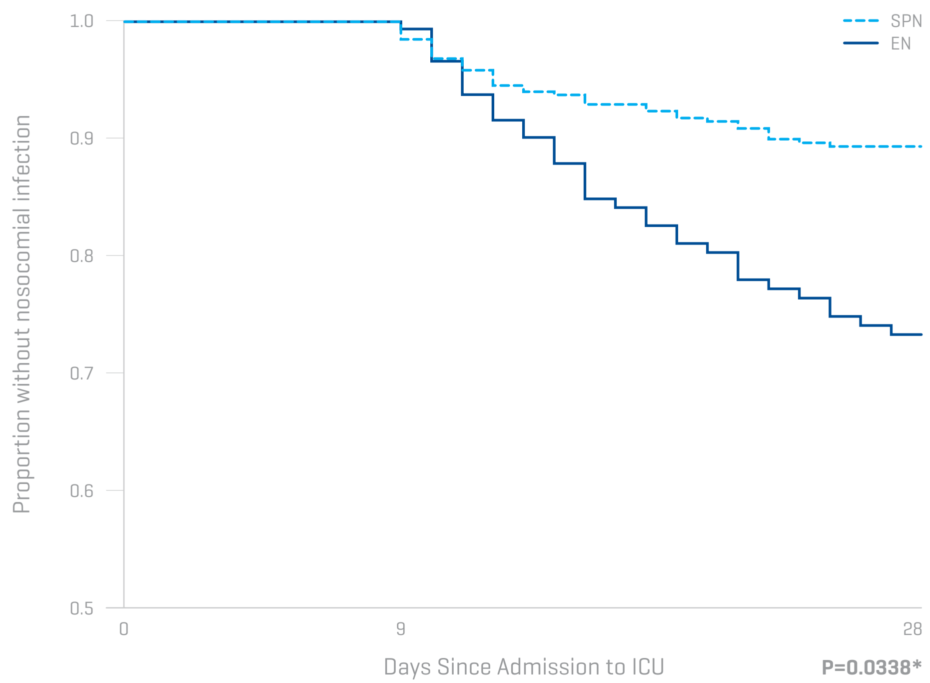
RESULTS

Twenty-seven percent of the patients in the SPN group (41 out of 153) developed a nosocomial infection versus 38 percent (58 out of 152) of patients in the EN group (hazard ratio 0.65, 95% CI 0.43–0·97; p=0.0338). The SPN group also had a lower mean number of nosocomial infections per patient (–0.42 [–0.79 to –0.05]; p=0.0248). In addition, during the follow-up period, patients in the SPN group were on antibiotics for less days than the EN group and had more antibiotic-free days. Mortality rates in the ICU and in general were similar between both groups.

CONCLUSIONS

Supplementing ICU patient energy targets with SPN starting on the fourth day of hospitalization could reduce nosocomial infections. This strategy should be considered as a method to improve clinical outcomes for critically ill patients in the ICU when EN is insufficient.

Kaplan-Meier Analysis of Nosocomial Infections



Number at Risk

SPN	153	148	99
EN	152	147	71

Figure 1 Twenty-seven percent of the patients in the SPN group (41 out of 153) developed a nosocomial infection versus 38 percent (58 out of 152) of patients in the EN group.
SPN=supplemental parenteral nutrition. EN=enteral nutrition.
*Statistically signifi cant with Benjamini-Hochberg correction.

Clinical Outcomes Related to Protein Delivery in a Critically Ill Population: A Multicenter, Multinational Observation Study

Nicolo M, Heyland D, Chittams J, Sammarco T, and Compher C. Clinical outcomes related to protein delivery in a critically ill population: a multicenter, multinational observation study. *JPEN J Parenter Enteral Nutr.* 2016 Jan;40 (1):45-51. doi: 10.1177/0148607115583675. Epub 2015 Apr 21.

LINK ▶

BACKGROUND

Patients benefit from optimal levels of energy and protein. However, data supporting outcomes associated with protein intake are limited. Studies have suggested that higher doses of protein can lessen the impact of catabolic losses in critically ill patients. Further, a greater protein intake has been associated with reduced infections, less days on the ventilator and lower mortality. Incomplete protein and/or energy provisions might play a role in muscle loss for patients in a catabolic state. Further data is needed to evaluate the actual impact of protein on mortality and time to discharge alive (TDA) for critically ill patients.

OBJECTIVE

The study aimed to analyze the impact of prescribed protein delivery on mortality and TDA using data from the International Nutrition Survey 2013. It was hypothesized that increased protein delivery would lead to lower mortality and decreased TDA.

METHODS

Existing data from the Improving Nutrition Practices in the Critically Ill International Nutrition Surveys 2013 was reviewed in a retrospective analysis. The database included 4,040 eligible patients from 202 sites, with the sample reviewed limited to patients who remained in the ICU for at least four days (2,828) and a sub-sample who were in the ICU at least 12 days (1,584). The four-day time frame was established to ensure there would be data on patient energy and protein provisions. Further, to be eligible the patients must have been mechanically ventilated within 48 hours of ICU admission. The database contained information on patients' mortality and TDA for 60 days after ICU admission.

For the purpose of this study, nutrition intake variables were the mean daily energy and protein delivery from all sources, such as enteral nutrition (EN), parenteral nutrition (PN), protein supplements and energy-containing medications, for up to 12 days. In addition, an "evaluable nutrition days" adjustment variable was created for the ≥4-day sample, because some patients may have had their protein and energy intake recorded for 4 days while others for 5 to 12 days. The percentage of protein intake delivered was determined by calculating the actual mean daily protein delivery over the evaluable nutrition days, with the reported prescribed protein intake on admission as a percentage. The same method was used to determine the patients' energy intake, as well.

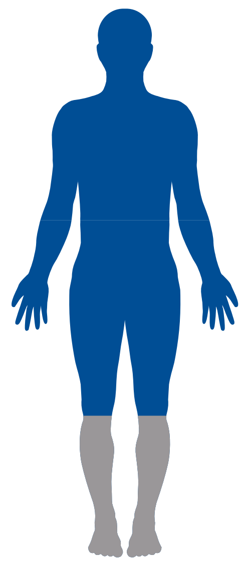
The protein and energy intake percentages were compared to the mortality outcomes using logistic regression and with Cox proportional hazards for TDA.

RESULTS

The mortality rate was lower for patients who consumed more protein. For the four-day sample group, the mean protein intake was 51 g (60.5% of prescribed) and 1,100 kcal (64.1% of prescribed). The 12-day sample group had a mean protein intake of 57 g (66.7% of prescribed) and 1,200 kcal (70.7% of prescribed). Patients who consumed ≥80% of prescribed protein goals benefited from reduced mortality (4-day sample: odds ratio [OR], 0.68; 95 percent confidence interval [CI], 0.50–0.91; 12-day sample: OR, 0.60; 95% CI, 0.39–0.93), while achieving ≥80% of prescribed energy intake was not associated with reduced mortality. In addition, while a protein intake of ≥80% of prescribed goals was not associated with a shorter TDA in the ≥4-day sample, it did predict a shorter TDA for the ≥12-day sample group. Achieving ≥80% of prescribed energy goals was associated with longer TDA for patients in the unadjusted (HR, 0.81; 95% CI, 0.71–0.94), adjusted (HR, 0.82; 95% CI, 0.71–0.96), and fully adjusted (HR, 0.81; 95% CI, 0.69–0.96) models for protein intake. The discharge rate for the ≥12-day group was not affected by energy delivery.

CONCLUSIONS

Patient survival and TDA are associated with patients achieving at least 80% of prescribed protein intake. Achieving at least 80% of prescribed energy intake was not associated with a positive impact on outcomes. The authors conclude that maximal efforts to achieve prescribed protein intake should be implemented in the ICU.



Nicolo et al. (2016) found at least **80% of prescribed protein intake** was associated with improved survival and **shorter time to discharge alive** in critically ill patients.

Optimal Protein and Energy Nutrition Decreases Mortality in Mechanically Ventilated, Critically Ill Patients: A Prospective Observational Cohort Study

Weijs P, Stapel S, de Groot S, Driessen R, de Jong E, Girbes A, Strack van Schijndel R, Beishuizen A. Optimal Protein and Energy Nutrition Decreases Mortality in Mechanically Ventilated, Critically Ill Patients: A Prospective Observational Cohort Study. *JPEN J Parenter Enteral Nutr.* 2012;36(1):60-8.

LINK ▶

BACKGROUND

Critically ill patients frequently do not consume optimal nutrition, which is proposed to be the provision of energy as determined by indirect calorimetry and protein of at least 1.2 g/kg. To improve patient nutrition, this study proposed identifying individual targets of energy and protein intake (optimal nutrition), achieving these targets and showing the targets are relevant to patient outcome.

OBJECTIVE

This prospective observational cohort study of 886 mechanically ventilated, critically ill patients using indirect calorimetry investigated if the nutrition-targeted (protein provision of at least 1.2 g/kg) approach had an effect on clinical outcome.

METHODS

From August 2004 to March 2010, the study took place in a mixed medical-surgical intensive care unit in an academic hospital and focused on patients who would need long-term intensive care. They were included in the study after their third to fifth day in the ICU if their predicted need for artificial nutrition would continue at least five to seven more days, indirect calorimetry measurement was performed, they were older than 18 and it was their first ICU stay with indirect calorimetry. Patients were excluded if they had FiO2 > 0.6, air leaks through cuffs and/or chest drains and metabolic monitor and/or personnel were unavailable.

Patients' caloric requirements were assessed with indirect calorimetry, and an algorithm was used to determine the nutrition formula and amount to be given during enteral nutrition. The enteral nutrition formulas used were: Numico's Nutrison Standard (total energy, 1,000 kcal/L; protein, 40 g/L) and Nutrison Protein Plus (1,250 kcal/L and 63 g/L) and Abbott Nutrition's Promote (1000 kcal/L and 63 g/L). Parenteral nutrition was an all-in-one admixture containing 1,000 kcal/L and 47 g/L of amino acids from an in-house pharmacy, which was later replaced by Fresenius-Kabi's mixture of 1,050 kcal/L and 50 g/L of amino acids.

Cox regression analysis was used to determine if achieving the protein and energy target had an effect on 28-day mortality, with adjustments for sex, age, body mass index, Acute Physiology and Chronic Health Evaluation II, diagnosis and hyperglycemic index.

RESULTS

Patients who reached their protein and energy target (PET) had a 14.7% 28-day mortality rate compared to patients who had no target (NT) and a 20.4% 28-day mortality rate. Setting and reaching energy and protein targets in mechanically ventilated, ICU patients resulted in a 50% decrease of 28-day hospital mortality compared to patients that do not reach either target.

Patients in the NT group had a shorter stay in the ICU, less total hospital days and decreased time on a ventilator, compared to patients who only reached their energy target (ET) and patients who hit their energy and protein goal (PET) by ($P < 0.05$). The group of patients who achieved only the protein target was not evaluated further due to the small number of patients in this group (n=24).

For the NT, ET and PET groups, energy intake was 75% ± 15 %, 96 % ± 5 %, and 99 % ± 5 % of target, and protein intake was 72 % ± 20 %, 89 % ± 10 %, and 112 % ± 12 % of target, respectively. Hazard ratios (95% confidence interval) for ET and PET patients were 0.84 (0.68-1.03) and 0.51 (0.33-0.78) for 28-day mortality, respectively.

CONCLUSIONS

Mechanically ventilated, critically ill patients who reached their protein and energy targets showed a 50% decrease in 28-day mortality compared to patients who did not reach either target. No reduction in mortality occurred for patients who reached only their energy targets.

Early High Protein Intake Is Associated With Low Mortality and Energy Overfeeding With High Mortality in Non-Septic Mechanically Ventilated Critically Ill Patients

Weijs P, Looijaard W, Beishuizen A, Girbes A and Oudemans-van Straaten H. Early high protein intake is associated with low mortality and energy overfeeding with high mortality in non-septic mechanically ventilated critically ill patients. *Critical Care.* 2014 Dec; 18:701.

LINK ▶

BACKGROUND

Observational studies of critically ill patients who consume 1.2 to 1.5 g/kg/day of protein have reported lower mortality; however, randomized studies investigating early protein feeding are needed as early high-protein intake may be harmful to patients with sepsis. A small observational study noted a link between higher protein intake and muscle wasting. Post-mortem muscle biopsies have shown impaired autophagy associated with the amount of infused amino acids. Further, delayed recovery was correlated with the cumulative amount of protein/amino acids consumed early during ICU stay, according to a post-hoc analysis of the EPaNIC (Early Versus Late Parenteral Nutrition in Critically Ill Adults) trial.

To study the effect of protein intake apart from energy intake, this study used several nutritional formulas with different protein/energy ratios and an algorithm to determine both energy and protein targets.

OBJECTIVE

This study aimed to prove: early protein intake of more than 1.2 g/kg according to ESPEN (European Society for Clinical Nutrition and Metabolism) guidelines was beneficial, early high-protein intake could be harmful to patients with sepsis and early energy over-feeding was harmful and might cloud the benefits of early high-protein intake. The researchers conducted a post-hoc analysis with new prospective observational data on early protein- and energy-intake on day four and their link to hospital mortality, particularly sepsis.

METHODS

A mixed medical-surgical ICU in a university hospital provided prospective observational data for the researchers to analyze post-hoc. The data covered the time frame of August 2004 to March 2010. Hemodynamically stable mechanically ventilated ICU patients were included in the study who had already been in the ICU for three to five days and were predicted to receive artificial nutrition at least another five to seven days. Patients also had indirect calorimetry during ICU admission, were older than 18 and had never been admitted to the ICU before. Disqualifying criteria was inspired oxygen fraction (FiO2) >0.6, air leakage and unavailable metabolic monitor data.

In the first 24 hours of ICU admission, hemodynamically stable patients were given early enteral nutrition (EN). This route was preferred over parenteral nutrition (PN), which was only given if the gut failed and not as supplementation to inadequate amounts of EN. The Harris and Benedict formula was initially used to calculate energy requirements with an added 10% for activity and 20% for stress, adjusted after indirect calorimetry was performed using a Deltatracmonitor. The energy target was the measured energy expenditure with an added 10% for activity, and protein was administered at 1.2 to 1.5 g/kg pre-admission body weight.

To determine the role of admission day-four protein intake (with cutoffs 0.8, 1.0 and 1.2 g/kg), energy overfeeding (ratio energy intake/measured energy expenditure > 1.1) and admission diagnosis of sepsis to hospital mortality (after adjustment for Acute Physiology and Chronic Health Evaluation II score), logistic regression analysis was used to examine their relationships.

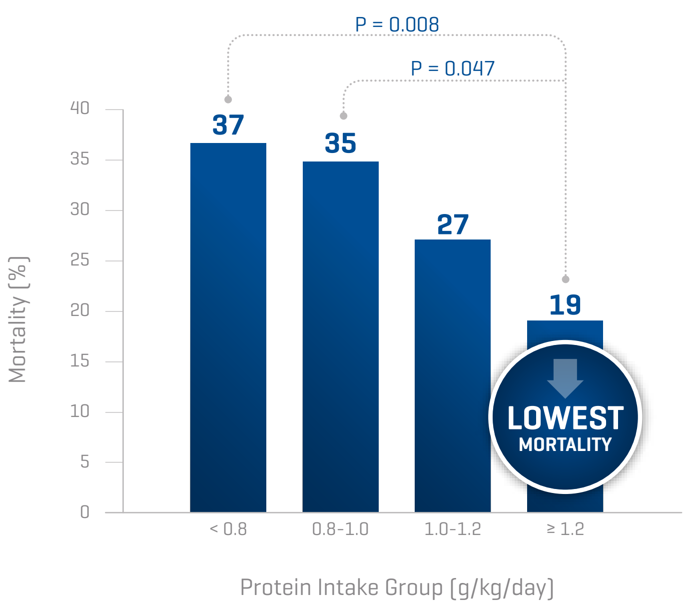
RESULTS

Early protein intake affects septic and non-septic patients differently. Of the 4,803 patients admitted to the ICU during the study period, 843 individuals fulfilled the inclusion criteria, with 117 having sepsis. Nutrition intake was fully enteral in 618 patients, fully parenteral in seven or mixed in 218 patients. At day four, overall (n=843) mean energy intake was 1,710 (699) kcal corresponding to 95% of measured energy expenditure. Mean day-four protein intake was 0.97 (0.49) g/kg pre-admission weight per day and hospital mortality was 36%. Day-four protein intake was not associated with mortality for patients with sepsis or energy overfeeding. For non-septic, non-overfed patients (n = 419), mortality decreased with higher protein intake group: 37% for <0.8 g/kg, 35% for 0.8 to 1.0 g/kg, 27% for 1.0 to 1.2 g/kg, and 19% for ≥1.2 g/kg (P = 0.033). For non-septic, non-overfed patients, a protein intake level of ≥1.2 g/kg was significantly associated with lower mortality (OR 0.42, 95%CI 0.21 to 0.83, P = 0.013).

CONCLUSIONS

Early high protein intake (≥1.2 g/kg at day four of ICU admission) was associated with lower mortality for non-septic, non-overfed critically ill patients, while early energy overfeeding was linked to higher mortality. Septic patients did not benefit from early high protein intake.

Early High-Protein Intake was Associated with Lower Mortality



Early Feeding at 10-20% Below Energy Target During the First 4 Days was Associated with Lower Mortality

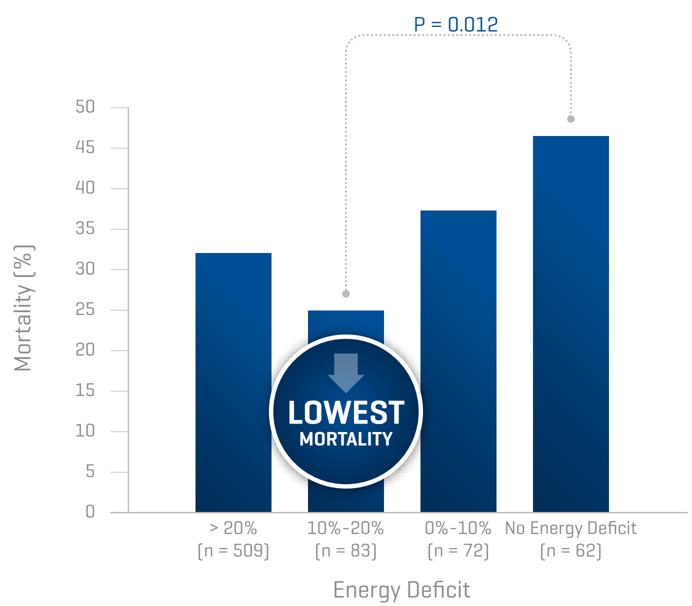


Figure 1 Non-septic, Non-overfed Critically Ill Patients
Adapted from Weijs P et al, Crit Care 2014

STUDY DESIGN

A prospective observational study of 843 ICU patients

- 117 Septic patients
- 307 Non-septic overfed patients
- 419 Non-septic, non-overfed patients
- Overfeeding was defined as a ratio between energy intake versus measured energy expenditure of >1.1

A Randomized Trial of Supplemental Parenteral Nutrition in Underweight and Overweight Critically Ill Patients: The TOP-UP Pilot Trial

Wischmeyer P, Hasselmann M, Kummerlen C, Kozar R, Kutsogiannis D, Karvellas C, Besecker B, Evans D, Preiser J, Gramlich L, Jeejeebhoy K, Dhaliwal R, Jiang X, Day A, Heyland D. A randomized trial of supplemental parenteral nutrition in underweight and overweight critically ill patients: the TOP-UP pilot trial. *Critical Care.* 2017; 21:142. doi: 10.1186/s13054-017-1736-8.

LINK ▶

BACKGROUND

International nutrition guidelines are not in agreement on the optimal amount of energy and protein for critically ill patients, and existing data remains inconclusive. In Europe, Canada and the United States, nutrition practice guidelines support enteral nutrition (EN) for critically ill patients who are hemodynamically stable, and recommend early initiation of EN in the ICU. Parental nutrition (PN) has also been used in 35 to 70% of critically ill patients, but current guidelines are not in agreement as to when it should be initiated. Early administration of energy and protein to ICU patients impacts patient mortality, especially for those with inadequate nutrition intake and body mass indices (BMIs) of <25 or >35, according to observational data.

OBJECTIVE

The purpose of this randomized trial was to see if supplemental parenteral nutrition (SPN) + EN in underweight and obese ICU patients would improve their 60-day survival rate and quality of life (QoL) compared to nutrition delivery via EN alone, which is usual patient care.

METHODS

From June 1, 2011 to January 20, 2015, an investigator-initiated, multi-center, randomized, controlled pilot trial was completed in 11 ICUs in Canada, the United States, Belgium and France. Adult ICU patients with acute respiratory failure who were expected to require mechanical ventilation for >72 hours and with a BMI of <25 or ≥35 were randomized to receive EN alone or SPN + EN to reach 100% of their prescribed nutrition goals for seven days after randomization. The goal of the pilot trial was that patients would achieve a 30% improvement in nutrition delivery.

The EN-alone control group received a formula selected by the individual treatment team based on their nutritional assessment, which was initiated at 20 mL/hr and increased by 20 mL/hr increments every four hours as tolerated until the energy goal was reached. The SPN+EN group was administered SPN through a central intravenous access as soon as possible. The PN solution used (3CB containing 9 g Nitrogen/L, Baxter Inc.) was also initiated at 20 mL/hr and increased every four hours by 20 mL/hr increments. Both the EN-alone and SPN+EN groups received the same prescription for calories and protein, with the study group consuming additional calories and protein via the parenteral route. The proposed target dose of protein and energy was based on patient BMI.

The primary outcome for the trial was to provide an increased calorie and protein delivery (about 30%) in the SPN+EN group compared to EN-alone. The investigators also analyzed calorie and protein delivery in patients with BMIs <25 and >35 and in surgical ICU patients versus medical ICU patients. Secondary outcomes included testing the SPN intervention, quality measures with protocol adherence and success in intervention delivery. In addition, other outcomes examined were ICU, hospital and 6-month mortality, infectious complications, length of mechanical ventilation, ICU stay and hospital stay. Functional indices were also assessed, such as admission and discharge Bartel Index, handgrip strength and a 6-minute walk test at discharge, including a three and six month post-randomization follow up into patients' vital status and 36-Item Short Form Health Survey (SF-36) scores.

RESULTS

No significant outcome differences were observed between the EN-alone and SPN+EN groups, including infection risks. Overall, 125 patients were enrolled out of 730 screened patients. The SPN group had increases in calorie and protein delivery of 26% and 22% (both p<0.001), respectively, versus EN alone. Further, surgical ICU patients received less nutrition via EN delivery and had a greater increase in calorie and protein delivery when receiving SPN versus medical ICU patients. Reduced hospital mortality, improved discharge functional outcomes and QoL outcomes were noted, although statistically insignificant, in the SPN+EN group compared to the EN-alone group.

CONCLUSIONS

The SPN+EN group significantly increased their calorie and protein delivery during their first week in the ICU compared to the EN-alone group, almost reaching a 30% increase in caloric delivery with no increased infection risk. It was feasible to deliver SPN+EN within the trial's prescribed protocol.

Resting Energy Expenditure, Calorie and Protein Consumption in Critically Ill Patients: A Retrospective Cohort Study

Zusman O, Theilla M, Cohen J, Kagan I, Bendavid I, Singer P. Resting energy expenditure, calorie and protein consumption in critically ill patients: a retrospective cohort study. *Critical Care.* 2016; 20:367,1-8.

LINK ▶

BACKGROUND

The optimal amount of nutritional support for critically ill patients is unclear. Most studies use predictive equations to assess caloric goals, which can be inaccurate when targeting energy intake. When caloric intake is increased to meet measured goals, both benefits and harm can be demonstrated. Further, underfeeding critically ill patients also leads to negative effects. Many ICU patients do not receive their full energy requirements and the proportion of calories delivered varies. Indirect calorimetry is a more accurate method of measuring resting energy expenditure, which can also provide updated data on changing energy requirements.

OBJECTIVE

The aim of this study was to examine how ICU patients fared in relation to their protein intake and percent of administered calories, divided by resting energy expenditure (% AdCal/REE) gathered from indirect calorimetry. ICU patient 60-day mortality, ICU length of stay and amount of time on mechanical ventilation were analyzed, as well.

METHODS

From 2003 to 2015, all ICU patients at the Rabin Medical Center who had IC measurements (Deltatrac II, Datex- Ohmeda, GE, USA) to assess caloric targets were included in the study. Patients also received enteral nutrition (EN) with or without supplemental total parenteral nutrition (TPN). Only patients with an ICU stay >96 hours or evaluable nutrition day were included in the main analysis, to eliminate any possible bias caused by short stay, early mortality or the expectation that the effect of nutrition might cause this duration of exposure.

Data on nutrition, protein intake and other variables came from a computerized system. Each patient's nutrition, such as the percent of daily administered calories divided by resting energy expenditure (% AdCal/REE) and the mean value for the ICU hospitalization, and its relationship to their 60-day mortality were evaluated. Sensitivity analyses were created to prevent any effects of the duration of exposure to nutrition on the results, such as only using measurements from day three onward, adjusting for total evaluable nutrition days and including patients who survived >7 days.

The study used a Cox proportional hazards model for 60-day mortality, and analyzed the connection between the % AdCal/REE (modeled to account for non-linearity) and length of stay (LOS) and length of ventilation (LOV).

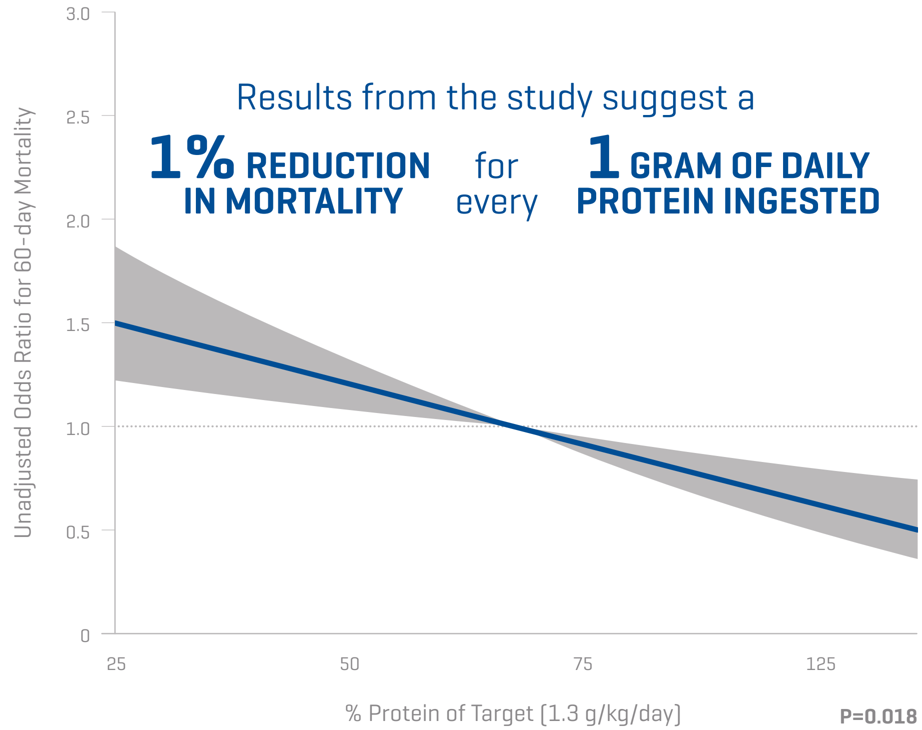
RESULTS

Patients' mortality, length of stay and length of ventilation were affected by energy and protein intake. Patients had a lower chance of dying if they consumed a specific amount of energy (up to 70%) and protein. Of the 6,994 patients admitted to the ICU during the testing period, 1171 patients were included in the final analysis. The % AdCal/REE had a significant non-linear (p < 0.01) association with mortality after adjusting for other variables (p < 0.01). Increasing the percent AdCal/REE from 0 to 70% resulted in reduced mortality with a hazard ratio (HR) of 0.98 (CI 0.97–0.99). However, an increase of more than 70% led to an increase in mortality with a HR of 1.01 (CI 1.01-1.02). The lowest mortality was noted at 70% AdCal/REE. Protein intake was also significantly associated with 60-day mortality (HR 0.99, CI 0.98–0.99, p = 0.02). The study found a linear association between protein intake and decreased mortality in the multivariable model (HR 0.99, 95% CI 0.98-0.99, p = 0.018), which suggests a 1% decrease in mortality for every gram of daily protein ingested and supports the importance of protein on improving survival. LOS and LOV appeared to increase if the AdCal/REE was >70%.

CONCLUSIONS

Patients' caloric goals require an exact estimate, such as from indirect calorimetry. Underfeeding and overfeeding can both be harmful to ICU patients. An increased LOS and LOV were associated with a higher caloric intake. However, an Adcal/REE of 70% gave patients a survival advantage. Increasing protein intake was associated with a decrease in 60-day mortality.

Association of Protein Intake with 60-day Mortality



Adapted from Zusman O, et al. Crit Care 2016;20:367-374[39]

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KIDNEY FUNCTION

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FUNCTIONAL OUTCOMES

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