Journal of Parenteral and Enteral Nutrition
Volume 39 Number 1
January 2015 13–20

DOI: 10.1177/0148607114528541
jpen.sagepub.com
hosted at
online.sagepub.com

Intensive Nutrition in Acute Lung Injury: A Clinical Trial (INTACT)

Carol A. Braunschweig, PhD, RD[1]; Patricia M. Sheean, PhD, RD[2]; Sarah J. Peterson, MS, RD[3]; Sandra Gomez Perez, MS, RD[4]; Sally Freels, PhD[5]; Omar Lateef, DO[6]; David Gurka, MD, PhD[6]; and Giamila Fantuzzi, PhD[1]

Abstract

Background: Despite extensive use of enteral (EN) and parenteral nutrition (PN) in intensive care unit (ICU) populations for 4 decades, evidence to support their efficacy is extremely limited. *Methods*: A prospective randomized trial was conducted evaluate the impact on outcomes of intensive medical nutrition therapy (IMNT; provision of >75% of estimated energy and protein needs per day via EN and adequate oral diet) from diagnosis of acute lung injury (ALI) to hospital discharge compared with standard nutrition support care (SNSC; standard EN and ad lib feeding). The primary outcome was infections; secondary outcomes included number of days on mechanical ventilation, in the ICU, and in the hospital and mortality. *Results*: Overall, 78 patients (40 IMNT and 38 SNSC) were recruited. No significant differences between groups for age, body mass index, disease severity, white blood cell count, glucose, C-reactive protein, energy or protein needs occurred. The IMNT group received significantly higher percentage of estimated energy (84.7% vs 55.4%, $P < .0001$) and protein needs (76.1 vs 54.4%, $P < .0001$) per day compared with SNSC. No differences occurred in length of mechanical ventilation, hospital or ICU stay, or infections. The trial was stopped early because of significantly greater hospital mortality in IMNT vs SNSC (40% vs 16%, $P = .02$). Cox proportional hazards models indicated the hazard of death in the IMNT group was 5.67 times higher ($P = .001$) than in the SNSC group. *Conclusions*: Provision of IMNT from ALI diagnosis to hospital discharge increases mortality. (*JPEN J Parenter Enteral Nutr*. 2015;39:13-20)

Keywords

fluids-electrolytes/acid-base; parenteral nutrition; nutrition; research and diseases

Enteral (EN) and parenteral nutrition (PN) support is provided to intensive care unit (ICU) patients under the assumption they will slow the loss of lean body mass (LBM) and improve outcomes.[1-3] Despite the extensive use of these feedings in critically ill populations for >4 decades, evidence to support their efficaciousness is extremely limited. A 2007 meta-analysis of prospective randomized clinical trials (RCTs) that compared EN with no EN or PN in a number of disease conditions, including critical care,[4] found almost no evidence of their benefit. Only 3 trials compared EN with no EN in critically ill populations,[5-7] and all were conducted in well-nourished, surgical ICU patients. No differences in mortality,[7] duration of time on the ventilator,[5,6] or length of stay (LOS) in the ICU[5] or hospital[7] were observed in these trials, suggesting that EN did not improve outcomes in normal nourished, surgical ICU patients.

We postulated that 3 major design flaws impeded the ability of these trials to discern the influence of nutrition support on clinically relevant outcomes. First, the conventional wisdom that feeding is always beneficial and withholding invasive nutrition support from malnourished patients is unethical resulted in their exclusion from most of these trials. The failure to demonstrate a positive benefit of EN on mortality or morbidity may, in part, be due to the restriction of only well-nourished participants in these trials. These individuals have little ability to show quantifiable benefit from EN. Second, the outcomes

From the [1]Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, Illinois, USA; [2]Loyola University, Chicago, Illinois, USA; [3]Department of Food and Nutrition, Rush University Medical Center, Chicago, Illinois, USA; [4]Institute for Health Policy and Research, University of Illinois at Chicago, Chicago, Illinois, USA; [5]Department of Epidemiology and Biostatitics, University of Illinois at Chicago, Chicago, Illinois, USA; and [6]Department of Medicine, Rush University Medical Center, Chicago, Illinois, USA

Financial disclosure: This research was funded by the NIH/NHLBI.

Received for publication December 18, 2013; accepted for publication February 26, 2014.

This article originally appeared online on July 11, 2014.

Corresponding Author:
Carol A. Braunschweig, PhD, RD, Department of Kinesiology and Nutrition, University of Illinois at Chicago, 1919 W Taylor (m/c 517), Room 650, Chicago, IL 60612, USA.
Email: braunsch@uic.edu

Download a QR code reader on your smartphone, scan this image, and listen to the podcast for this article instantly. Or listen to this and other *JPEN* podcasts at http://pen.sagepub.com/site/misc/Index/Podcasts.xhtml.

selected to assess efficacy in these previous trials take many days of adequate nutrition intake to alter their course of development, yet the nutrition interventions were generally of short duration (7–10 days). Finally, participants randomized to the intervention groups were provided with an aggressive, invasive EN and/or PN during the catabolic phase of their hospitalization under the assumption it would slow the loss of LBM; repletion is not possible during this interval. The nonvolitional interventions were discontinued when the critical illness resolved. Repletion with adequate nutrient intake is possible during this interval; however, participants reverted to standard nutrition care with little attention to adequacy. This "nutrition feast" during the phase of illness when repletion is not possible, followed by "famine" during the interval when recuperation is possible, resulted in all participants receiving poor intake postrandomization. These previous designs likely attenuated the abilities to detect differences in any nutrition-related post-ICU outcomes examined, such as LOS or total infections while hospitalized.

Because of these limitations in previous trials, we designed and conducted an RCT to determine if a comprehensive nutrition program from acute lung injury (ALI) diagnosis to hospital discharge could improve morbidity and influence mortality in normal and malnourished ICU patients. Patients with ALI were selected because they typically have functional gastrointestinal tracts and a high prevalence of malnutrition. We hypothesized that patients randomized to receive the intensive medical nutrition therapy (IMNT) intervention would have fewer infections, shorter hospital and ICU LOS, and lower mortality than those randomized to standard nutrition support care (SNSC).

Overview, Study Design, and Patient Recruitment

This single-center RCT was originally designed to detect the influence of the provision of IMNT from ALI diagnosis to hospital discharge compared with SNSC on nosocomial infections in ICU patients. Secondary endpoints included days to weaning from mechanical ventilation, ICU and hospital LOS, and death. Adult (≥18 years) patients were recruited from the medical or surgical ICUs of an urban tertiary care hospital with a diagnosis of ALI, as defined by the American-European Consensus Conference (AECC).[8] To improve internal validity and control disease acuity, patients were excluded if they were previously admitted to the ICU during the same hospitalization, had medical orders not to resuscitate, were severely immunosuppressed (eg, post–stem cell transplant, receiving chemotherapy), or had immobility or severe neurologic disease prior to admission. Within 24 hours of ALI diagnosis, patients meeting eligibility criteria were approached for participation. A written informed consent was obtained from the participant or a designated surrogate prior to enrollment, an identification number was assigned, and randomization to either SNSC or IMNT occurred. Feeding group assignment was determined using a computer-generated list of random numbers, and group assignments (IMNT or SNSC) were placed in sequentially numbered, sealed opaque envelopes prior to the start of the trial. When notified of a new enrollment, a non–hospital-based research member, blind to all aspects of the participant's profile, opened the envelope and informed the hospital-based personnel of the participant's assigned feeding group. Ethical approval for this study was granted by the Medical Center's and University's Institutional Review Boards, and the study was conducted between 2009 and 2013.

Standard Nutrition Support Care

Participants randomized to SNSC received the nutrition care provided by their physicians and registered dietitians (RDs). The protocol for SNSC includes nutrition assessments completed by an RD and feeding recommendations conveyed in daily multidisciplinary patient care rounds and via the electronic medical record, specifying formula, type of feeding (eg, bolus, intermittent, or continuous), initiation rate, and goal infusion. All enteral feeding devices were placed by the medical service, and EN was administered at the discretion of the attending service. Per the ICU EN feeding protocol, nursing staff members held EN if gastric residual volumes exceeded 250 mL during a 4-hour infusion period, vomiting occurred, or aspiration was suspected. As deemed appropriate by the attending service, PN was initiated when patients could not be fed via the enteral route within 72–96 hours of intubation. All efforts to transition patients from PN to EN were completed following the institutional protocols. Following extubation, oral diets were initiated and prescribed by the managing medical services. Snacks, multivitamin supplements, and dietary counseling were provided only when ordered.

IMNT Intervention

Participants randomized to IMNT received all of the SNSC practices described above; however, several factors did specifically differ. First, EN tubes were placed more rapidly, and EN was initiated within 6 hours of hemodynamic stability. Second, to improve overall energy provision, the following changes were made: (1) EN infusions received were closely monitored, and rates were increased to achieve estimated daily needs when feeding interruptions occurred, and (2) feedings were prescribed during a 24-hour period (eliminating bolus or intermittent feeding prescriptions). To avoid the complications of prolonged overfeeding, EN volumes were reviewed on a daily basis and altered as needed to match estimated energy needs. Following extubation, oral dietary intake was initiated as soon as swallowing allowed. Increased dietary intake was facilitated by eliminating unnecessary therapeutic dietary prescriptions, assisting with feeding, and providing increased snacking options and meal tickets for cafeteria purchases. In addition,

the study staff visited the participant during meal times to address and resolve specific feeding issues and to discuss the importance of eating during recovery.

Energy and Protein Estimations and Intake

The use of indirect calorimetry is considered the gold standard for energy needs assessment; however, because of the prohibitory percentages of fraction of inspired oxygen (ie, >50%) and the frequency of weaning trials for extubation, this was impractical in this patient population. Therefore, energy prescriptions were calculated using 30 kcal/kg admission weight or obesity-adjusted ideal body weight.[9] Protein prescriptions were estimated using 1.5 g protein/kg ideal body weight for patients without obesity and using adjusted ideal body weight for patients with obesity.[9-11] Measurement of energy and protein intake was assessed from physician orders and nursing graphics for daily EN and/or PN received and multivitamin/mineral supplements consumed. EN data included the formula name and composition and daily volume ordered and received. The daily PN prescription (percentage carbohydrate, protein, and fat) ordered and received was recorded. Because propofol was used for used for sedation, the caloric contributions of this lipid-based medication were also included in the total energy intake, as appropriate. All energy provided via dextrose-containing IV fluids was also included in the total energy intake. As previously described, study personnel obtained calorie counts for all participants using a multiple-pass 24-hour recall approach.[12] Briefly, menus were saved for each meal and reviewed with all of the participants and/or family members each day. Patients were asked to recall everything they had consumed at each of the meals. Clarification was sought for any food mentioned but not on the menu or any food that was not listed but appeared on the menu. Foods consumed between meals were also recorded. Upon collection of daily oral intake, the energy and protein content of all food items prepared/provided by the institution were obtained from the institutions Food and Nutrition Services nutrient analysis; the nutrient content of foods consumed that were not provided by the institution (ie, food consumed from family/friends) was calculated using the University of Minnesota Nutrient Data System for Research.

Demographics and Clinical Variables

Demographic and medical information including gender, race/ethnicity, age, diagnosis, and admission height and weight were collected from the electronic medical record. Body mass index (BMI) was calculated based on admission weight (kg)/height $(m)^2$. The Acute Physiology and Chronic Health Evaluation (APACHE) II score upon ICU admission was used to assess the severity of illness.[13] These scores range from 0–71, with higher scores indicating more severe illness. The Sequential Organ Failure Assessment (SOFA) scores[14,15] assessed daily from enrollment to ICU discharge were used to characterize participants' organ function while critically ill. These scores (range, 0–24) are based on an individual's respiratory, cardiovascular, hepatic, coagulation, renal, and neurologic systems; higher scores indicated more severe organ compromise. Nutrition status was assessed at baseline using the Subjective Global Assessment (SGA).[16] Use of steroids, vasopressors, or inotropic agents and the number of transfusions of packed red blood cells and platelets were also recorded.

Venous bloods draws occurred daily between 6:00 and 8:00 AM. Participants' white blood cell count per unit volume (nL range, $4.50–11.0 \times 10^9$/L), high and low serum glucose (mg/dL) levels, and baseline C-reactive protein level (mg/dL) were recorded. The hyper- and hypoglycemic events were defined as blood glucose levels >180 mg/dL or <60 mg/dL, respectively, based on the results from the 2009 NICE Sugar Study.[17] Infections were determined according to the International Sepsis Forum definitions for ICU infections.[18] Positive cultures for general skin organisms that may represent contaminants (ie, coagulase-negative *Staphylococcus* or non-JK group *Corynebacteria*) were not included unless they were isolated from at least 2 blood cultures drawn within 24 hours of each other and treated by the physician.

Power analysis and sample size calculations were performed using Power Analysis and Sample Size (NCSS Statistical and Power Analysis Software, PASS, 2005) for the log-rank test[19] based on findings reported by Rubinson et al.[20] They reported an overall bloodstream infection rate of 22% (31/138 patients) in adults unable to consume an oral diet in their first 96 hours after admission to the medical ICU. Patients who received 25% or more of their estimated energy needs had significantly lower risks for infections than patients who received <25% of estimated needs (relative hazard, 0.24; 95% confidence interval [CI], 0.1–0.6; adjusted for APACHE II relative hazard, 0.27; 95% CI, 0.11–0.68). On the basis of these results, and a significance level of 5%, a sample size of 200 (100/group) provided 87% power to detect a hazard ratio (HR) of 2.5 or more and was the recruitment goal for this trial.

Statistics

Standardized descriptive statistics including measures of means, median, standard deviations, ranges, and standard errors for continuous variables were calculated to describe the groups. For dichotomous variables (eg, hypo- or hyperglycemia, infections, death), χ^2 tests were used to obtain unadjusted comparisons between the 2 groups, and Student t tests and Wilcoxon rank-sum tests were used for unadjusted comparisons of continuous variables (eg, number of infections, energy and protein intake per day, days on mechanical ventilation) that were normally and nonnormally distributed, respectively. Time until infections, ICU and hospital discharge, and death was estimated within groups using survival analysis methods, treating discharge alive or death as right-censoring. The cumulative

Table 1. Demographic Profile and Baseline Clinical Parameters of Participants (N = 78).[a]

Variable	Intervention (n = 40)	Control (n = 38)	*P* Value
Age, y	52.5 (17.1)	58.6 (16.2)	.11
Female, n (%)	21 (51.2)	17 (44.7)	.56
Race, n (%)			.88
African American	10 (25)	11 (29)	
Caucasian	22 (55)	18 (47)	
Hispanic	8 (20)	9 (24)	
Height, cm	170.1 (10.5)	170.7 (10.1)	.81
Weight, kg	86.3 (27.6)	88.6 (27.2)	.71
Body mass index, kg/m^2	29.8 (9.3)	30.1 (8.9)	.89
BMI ≥30, n (%)	18 (45)	18(47)	.83
SGA category, n (%)			.15
Normal	27 (65.8)	23 (60.5)	
Moderate	11 (26.8)	15 (39.5)	
Severe	3 (7.3)	0	
Baseline SOFA	9.3 (3.8)	9.4 (3.4)	.97
APACHE II	23.4 (9.3)	27.7 (7.9)	.03
PaO_2:FiO_2 ratio	195 (105)	183 (122)	.69
PaO_2:FiO_2 ratio ≤200, n (%)	23 (58)	21 (55)	.84
CRP, mg/dL	102.2 (92.2)	131.2 (92)	.20
White blood cell count, cells × 10^9/L	13.3 (12.2)	11.1 (6.2)	.34
Glucose, mg/dL	154 (48.9)	150.9 (55.1)	.78

APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; CRP, C-reactive protein; SGA, Subjective Global Assessment; SOFA, Sequential Organ Failure Assessment.
[a]Values are means (standard deviations) unless otherwise indicated.

incidence of death was estimated within groups using the Kaplan-Meier method. Unadjusted comparisons between the groups were made using the log-rank test, and Cox proportional hazards multiple regression was used to adjust for additional factors including BMI, age, gender, SOFA, APACHE II, ethnicity, total and daily dose of insulin, and number of hyper- and hypoglycemic days, PN, and/or parenteral lipids. All analyses were done using the statistical program SAS (version 9.2, 2009, SAS Institute Inc, Cary, NC).

Interim safety analysis was planned every time 25 additional patients were added per group (ie, 4 times total until 100 per group were enrolled) using sequential testing methods described by Pocock.[21] It was determined that a critical *P* value of $\alpha' = .0182$ for each sequential test provided an overall type I error rate of $\alpha = .05$. Specific outcomes compared included number of infections, length of hospital stay, number of days on mechanical ventilation, death, and adverse events associated with nutrition support. The independent data safety monitoring board reviewed each of the interim safety analyses and advised for trial continuation or stopping.

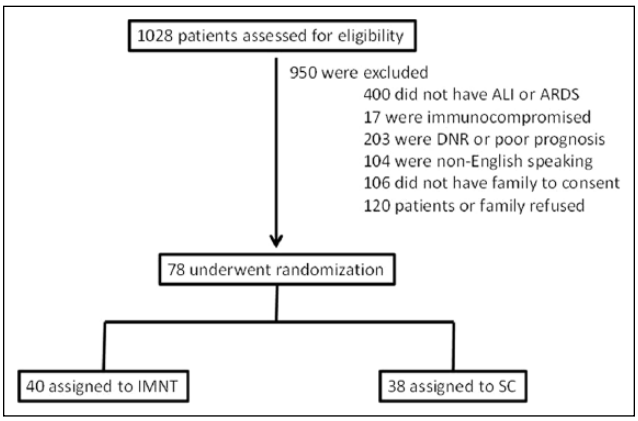

Figure 1. Enrollment and randomization of participants.

Results

A total of 1028 patients who required mechanical ventilation between July 10, 2009, and May 1, 2013, were evaluated for potential study enrollment. The reasons for exclusion and randomization into IMNT or SNSC are depicted in Figure 1. The demographic and baseline clinical parameters of the 78 participants who were enrolled (40 IMNT, 38 SNSC) are provided in Table 1. Overall, participants had a mean (SD) age of 55.4 (17) years, were predominantly obese, and approximately 37% were classified as malnourished (moderate or severe) by SGA. No differences in age, gender, race/ethnicity, BMI, nutrition status, baseline SOFA score, PaO_2:FiO_2 ratio, proportion of participants with PaO_2:FiO_2 <200, baseline C-reactive

Table 2. Nutrition Requirements and Amount of Energy/Protein Received per Day.[a]

Variable	Intervention (n = 40)	Control (n = 38)	*P* Value
Estimated energy needs, kcal	2158 (426)	2219 (342)	.48
Estimated protein needs, g	109 (20)	111 (17)	.59
Energy received/d, kcal	1798 (509)	1221 (423)	<.0001
Percentage of estimated energy needs received per day	84.7 (22)	55.4 (19)	<.0001
kcal/kg received per day[b]	25.4 (6.6)	16.6 (5.6)	<.0001
Received PN, n (%)	8 (20)	5 (13.2)	.42
Mean days of PN intake among participants who received PN	6.4 (5.2)	6.0 (4.1)	.89
Protein received per day, g	82 (23)	60.4 (24)	<.0001
Percentage of estimated protein needs received per day	76.1 (18)	54.4 (21)	<.0001
Received parenteral lipids,[c] n (%)	13 (32)	5 (13)	.09

[a]All data are means (SD).
[b]Kcal/kg = kcal/kg admit weight or adjusted ideal body weight if body mass index ≥30 kg/m^2.
[c]Includes lipids from parenteral nutrition and propofol.

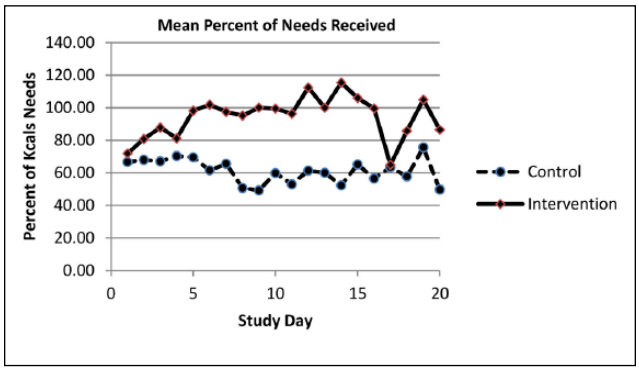

Figure 2. Mean percentage of energy needs received per day in the intensive medical nutrition therapy (Control) and standard nutrition support care (Intervention) groups.

protein, white blood cell count, or glucose levels occurred between the groups. The APACHE II score at ICU admission was significantly lower in the IMNT than in the SNSC group (23.4 vs 27.7, respectively, $P = .03$).

The estimates of energy and protein needs and the percentage of estimated needs received per day in the IMNT and SNSC groups are depicted in Table 2. Energy and protein requirements were similar between groups. Participants randomized to IMNT received significantly greater percentages of estimated energy and protein needs per day throughout the study and significantly greater kcal/kg/d (Table 2; Figure 2). No significant differences in the number of participants/group who received PN (8/40 IMNT vs 5/38 SNSC, $P = .42$), the mean number of days of PN in participants who received any PN, or the overall percentage of energy received per day from PN (9% intervention, 7% control, $P = .33$) were found. The percentage of participants who received parenteral lipids as propofol or via their PN prescription also did not differ between groups (32% IMNT, 16% SNSC, $P = .09$)

Study outcomes are presented in Table 3. Overall, there was no difference between groups in hospital or ICU LOS, number of days on mechanical ventilation, infections, or number of days between hospital admission and study enrollment day. The mean amount of insulin received was similar between groups; however, when analysis was restricted to the days insulin was received in participants who received any insulin (17/40 intervention and 20/38 controls), significantly more insulin per day was received by the IMNT compared with the SNSC group (78 vs 36 U/d, $P = .03$). In June 2013, a review by the Data Safety Monitoring Board revealed significantly more deaths in the IMNT compared with the SNSC group (16/40 [40%] vs 6/38 [16%], $P = .017$). Although no apparent differences were observed for cause of death between the 2 groups, the recent reports of worse outcomes in participants randomized to receive higher energy intake compared with controls in 3 large well-designed RCTs similar to INTACT,[22-25] coupled with the highly significant differences in death rates, resulted in the recommendation by the Data Safety Monitoring Board to end the trial.

The Kaplan-Meier estimates of time to death and log-rank test for unadjusted comparisons between the groups are presented in Figure 3. The first death in the IMNT group occurred on study day 4, and 7 deaths had occurred by day 10. The first death in the SNSC group did not occur until study day 11. Estimates of the HR for death and its confidence intervals in the IMNT vs SNSC groups assessed with Cox proportional hazards multiple regression analysis are presented in Table 4. Baseline parameters evaluated for inclusion in the model were BMI, age, gender, race/ethnicity, SGA, SOFA, and APACHE II scores. Unadjusted analysis revealed that participants in the IMNT group experienced a 2.65 times higher hazard of death than those randomized to SNSC. When adjusted for age (HR, 1.04; 95% CI, 1.02–1.07; $P = .001$) and baseline SOFA score (HR, 1.32; 95% CI, 1.14–1.54; $P = .0003$), the hazard of death in the IMNT group was 5.67 times ($P = .001$) higher than in the SNSC group. No other baseline variables evaluated (including

Table 3. Clinical Outcomes in IMNT vs SNSC Participants (N = 78).

Variable	IMNT (n = 40)	SNSC (n = 38)	*P* Value
Hospital LOS, d	27.2 (18.2)	22.8 (14.3)	.33
ICU LOS, d	15.5 (12.8)	16.1 (11.5)	.83
Number of days between hospital admission and enrollment	8.8 (8.7)	6.4 (6.6)	.17
Days on ventilator (median, IQR)	6 (4–10)	7 (3–14)	.85
Number of infections, n (%)	5 (12)	8 (21)	.29
Any hyperglycemic event, n (%)[a]	30 (73)	26 (68)	.64
Number of days with hyperglycemia	2.2 (3.0)	2.4 (4.0)	.85
Any hypoglycemic event, n (%)[a]	12 (29.3)	11 (28.9)	.98
Number of days with hypoglycemia	0.3 (0.6)	0.9 (0.7)	.08
Insulin received per day, U	23.6 (47.6)	14 (23.6)	.25
Insulin received per day on days insulin was received in participants who were given insulin, U	77.7 (70.4)	35.9 (27.9)	.03
Died	16 (40.0)	6 (15.8)	.017

All values are mean (SD) unless otherwise indicated. ICU, intensive care unit; IMNT, intensive medical nutrition therapy; IQR, interquartile range; LOS, length of stay; SNSC, standard nutrition support care.
[a]Hyperglycemia defined as glucose >180 mg/dL; hypoglycemia defined as glucose <70 mg/dL.

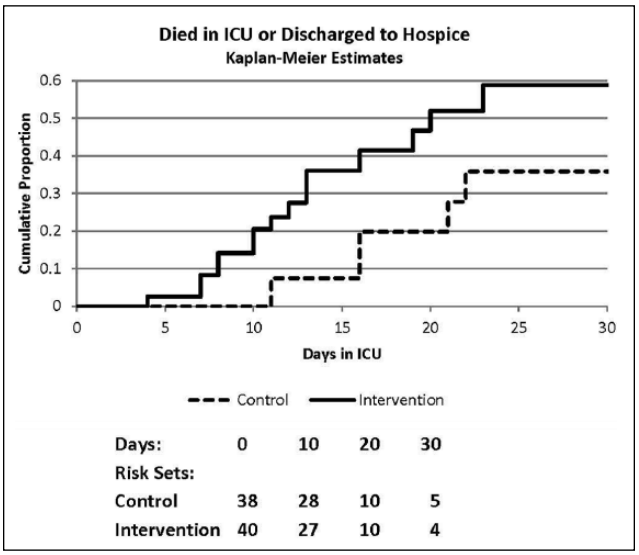

Figure 3. Kaplan-Meier estimates of time to death and log-rank test results for unadjusted comparisons between intensive medical nutrition therapy and standard nutrition support care.

BMI, gender, race/ethnicity, SGA, or APACHE II) were found to be significant additional predictors during Cox modeling.

Discussion

Current Canadian, European, and U.S. guidelines for nutrition support of ICU patients recommend early EN initiation (within 24–48 hours).[1-3] The major findings from this RCT demonstrate that providing IMNT from ALI diagnosis to hospital discharge to ICU patients resulted in 5.67 times greater hazard of death in the IMNT group ($P = .001$) compared with the SNSC group when adjusted for baseline age and SOFA score. These findings are similar to 3 recent large, well-designed RCTs that found superior outcomes (ie, lower infection rates, shorter hospital and ICU stays, and better survival) in those randomized to lower vs higher nutrient intakes in the first ~7 days of ICU stay.[22,23,25] Casaer et al[23] compared ICU patients (medical and surgical) randomized to full feeding via EN/PN (n = 2312) in the first 7 days of ICU admission to those who did not receive PN during this interval (n = 2328). They found fewer ICU infections and greater likelihood of discharge alive from the ICU in patients who did not receive PN. Post hoc analysis indicated that the lowest dose of macronutrients received was associated with the fastest recovery, regardless of route (ie, PN or EN), and protein rather than glucose appeared to explain the results.[24] Further, a subset of patients (n = 517) who were randomized to late PN and could not receive EN (ie, these patients received essentially no nutrition for the first week) had lower infection rates (29.9% vs 40%, $P = .01$) and a 20% greater likelihood of ICU survival (HR, 1.2; 95% CI, 1.00–1.44; $P = .05$) than those receiving early EN/PN. Arabi et al[22] randomized medical/surgical ICU patients (n = 240) to EN at estimated energy requirements vs permissive underfeeding. Significantly higher hospital mortality occurred in patients randomized to target compared with underfeeding regimens (42.5% vs 30%, relative risk [RR], 0.71; 95% CI, 0.50–0.99; $P < .05$). Singer et al[25] also reported negative outcomes from greater energy exposure in their single-center RCT in patients (N = 130) expected to require mechanical ventilation for at least 72 hours. They found that mechanical ventilation (16.1 ± 14.7 vs 10.5 ± 8.3 days, $P < .05$), ICU LOS (17.2 ± 14.6 vs 11.7 ± 8.4 days, $P < .05$), and total infection complications ($P < .05$) were higher in the intervention vs control group; however, there was a trend for lower hospital mortality in the intervention group ($P = .058$).

Table 4. Cox Regression Analysis Relating IMNT vs SNSC and Adjusted for Other Clinical Characteristics to Death.

Independent Variable	Hazard Ratio	95% CI	*P* Value
Model 1			
IMNT vs SNSC	2.65	1.03–6.84	.04
Model 2			
IMNT vs SNSC	5.67	1.97–16.29	.001
Age	1.04	1.01–1.08	.001
Baseline SOFA	1.32	1.11–1.57	.003

CI, confidence interval; IMNT, intensive medical nutrition therapy; SOFA, Sequential Organ Failure Assessment; SNSC, standard nutrition support care.

Although each of these studies has investigated different ICU populations and varied in timing and type of nonvolitional feedings provided, collectively, their findings challenge the national and international nutrition support recommendations for early EN feeding in ICU patients.

Our trial was stopped prior to meeting enrollment goals because of greater mortality in the IMNT group. The data presented in Table 1 indicate randomization was effective in equally distributing patients based on age, BMI, nutrition status, SOFA score, PaO_2:FiO_2 ratio, and biochemical measures for glucose and inflammation. The intervention successfully delivered significantly greater percentages of estimated energy and protein needs per day to the IMNT vs SNSC group. Specifically, the IMNT group received 84.7% of their estimated needs per day, which averaged 25.4 (6.6) kcal/kg/d compared with 55.4% and 16.6 (5.6) kcal/kg/d in the SNSC group ($P < .0001$). The differences in intake between groups began at enrollment and continued throughout the trial. All of the RCTs described in the preceding paragraph used different predictive equations or dosing weights to estimate requirements, and only 1 investigation[22] reported the average kcal/kg received in their participants, limiting the ability to make comparisons between the studies. Two other recent studies[26,27] found no difference in outcomes between study groups; however, calorie delivery among subjects in their intervention groups were was actually closer to the control groups of Singer et al,[25] Casaer et al,[23] and our trial. We speculate that our effectiveness in delivering daily goal energy intake early after ALI diagnosis and consistently in our IMNT patients contributed to their higher mortality rates compared with those in other RCTs.

The first death in our IMNT group occurred on study day 4, and 7 of the 16 deaths (44%) occurred by day 10. In the SNSC group, the first death occurred on day 11. This suggests early exposure to higher energy intake in the IMNT group, rather than overall intake, increased their mortality rates compared with SNSC. The infusion of nonvolitional highly refined feedings, delivered over 24 hours, has been postulated to interfere with autophagy (ie, cellular cleaning), to adversely affect gut microbiota, and to impair immune response.[24,28-30] Our findings support these hypotheses and the need for trials to investigate these proposed mechanisms.

EN is an artificial mode of nutrition provision. It is infused in ICU populations under the assumption that it will slow LBM loss and improve outcomes.[1,3,31] Our findings and other recent RCTs suggest withholding nonvolitional nutrition during the acute phase of illness may be beneficial. A true control group (ie, no EN or PN) was not included in any of these trials, so it is unknown if eliminating EN/PN would have influenced results. No RCT in an ICU population has assessed the influence of PN or EN on changes in LBM and its subsequent influence on outcomes; thus, it is unknown if this link exists. Enteral feeding is a medical intervention with inherent risks and costs[32-36] and should not be equated with the oral consumption of food. It is biologically feasible that withholding nonvolitional EN/PN until the catabolism of critical illness has resolved has no negative effect and that the natural physiologic response of anorexia and loss of appetite due to cytokine-producing disease is indeed beneficial.

Our study has certain limitations that merit consideration. First, it was a small single-center trial that was stopped early because of higher mortality rates in the IMNT group. Our final sample size was underpowered to detect differences in infection rates, which were our a priori primary outcome. Second, we used energy and protein equations that provided only estimates of nutrition needs. Nutrition is provided to support the maintenance of LBM, and presumably, patients classified as normally nourished would have healthy levels of lean mass. However, using computed tomography, we recently reported that SGA was unable to detect low levels of LBM in critically ill individuals. Thus, while our nutrient estimates were conservative (30 kcal/kg) and participants in the IMNT group received approximately 25 kcal/kg provision (a widely accepted level for estimating basal energy needs), this level may have resulted in overfeeding in the intervention group. Studies using indirect calorimetry combined with accurate body composition methodologies are needed to more accurately assess and guide nutrient delivery in a research setting. Finally, while these results are generalizable to patients with ALI, they should not be extrapolated to all critically ill patients in the medical ICU or to populations in other ICUs.

In conclusion, we found that IMNT provided from ALI diagnosis to hospital discharge resulted in greater mortality compared with SNSC. These findings are similar to other recent trials in ICU populations and challenge the current national ICU feeding guidelines. Our a priori hypotheses did

not include any postenrollment subgroup analyses of events that may have influenced mortality. We anticipate conducting post hoc secondary analysis of our data to address the important new questions that have been raised by our findings. Ultimately, all human beings will die from starvation if nutrition is withheld indefinitely. Future RCTs of nonvolitional feeding during acute illness tailored to discern the optimal method, dose, timing, and influence on mechanistic outcomes are badly needed.

Author(s) Note

ClinicalTrials.gov registration number 01921101.

References

1. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2009;33(3):277-316.
2. Dhaliwal R, Cahill N, Lemieux M, Heyland DK. The Canadian Critical Care Nutrition Guidelines in 2013: an update on current recommendations and implementation strategies. *Nutr Clin Pract*. 2014;29(1):29–43.
3. Singer P, Berger MM, Van den Berghe G, et al. ESPEN guidelines on parenteral nutrition: intensive care. *Clin Nutr*. 2009;28(4):387-400.
4. Koretz RL, Avenell A, Lipman TO, Braunschweig CL, Milne AC. Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. *Am J Gastroenterol*. 2007;102(2):412-429.
5. Hasse JM, Blue LS, Liepa GU, et al. Early enteral nutrition support in patients undergoing liver transplantation. *JPEN J Parenter Enteral Nutr*. 1995;19(6):437-443.
6. Dvorak MF, Noonan VK, Belanger L, et al. Early versus late enteral feeding in patients with acute cervical spinal cord injury: a pilot study. *Spine*. 2004;29(9):E175-E180.
7. Moore EE, Jones TN. Benefits of immediate jejunostomy feeding after major abdominal trauma—a prospective, randomized study. *J Trauma*. 1986;26(10):874-881.
8. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 pt 1):818-824.
9. Krenitsky J. Adjusted body weight, pro: evidence to support the use of adjusted body weight in calculating calorie requirements. *Nutr Clin Pract*. 2005;20(4):468-473.
10. Ishibashi N, Plank LD, Sando K, Hill GL. Optimal protein requirements during the first 2 weeks after the onset of critical illness. *Crit Care Med*. 1998;26(9):1529-1535.
11. Shaw JH, Wildbore M, Wolfe RR. Whole body protein kinetics in severely septic patients: the response to glucose infusion and total parenteral nutrition. *Ann Surg*. 1987;205(3):288-294.
12. Peterson SJ, Tsai AA, Scala CM, Sowa DC, Sheean PM, Braunschweig CL. Adequacy of oral intake in critically ill patients 1 week after extubation. *J Am Diet Assoc*. 2010;110(3):427-433.
13. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13(10): 818-829.
14. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22(7):707-710.
15. Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care: results of a prospective, multicentre study. Working Group on Sepsis Related Problems of the ESICM. *Intensive Care Med*. 1999;25(7):686-696.
16. Baker JP, Detsky AS, Whitwell J, Langer B, Jeejeebhoy KN. A comparison of the predictive value of nutritional assessment techniques. *Hum Nutr Clin Nutr*. 1982;36(3):233-241.
17. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
18. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. *Crit Care Med*. 2005;33(7):1538-1548.
19. Collett D. *Modelling Survival Data in Medical Research*. 2nd ed. Boca Raton, FL: Chapman & Hall/CRC; 2003.
20. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med*. 2004;32(2):350-357.
21. Pocock SJ. Randomised clinical trials. *Br Med J*. 1977;1(6077):1661.
22. Arabi YM, Tamim HM, Dhar GS, et al. Permissive underfeeding and intensive insulin therapy in critically ill patients: a randomized controlled trial. *Am J Clin Nutr*. 2011;93(3):569-577.
23. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506-517.
24. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. *Am J Respir Crit Care Med*. 2013;187(3):247-255.
25. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med*. 2011;37(4):601-609.
26. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795-803.
27. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA*. 2013;309(20):2130-2138.
28. Vanhorebeek I, Gunst J, Derde S, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. *J Clin Endocrinol Metab*. 2011;96(4):E633-E645.
29. Derde S, Vanhorebeek I, Guiza F, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. *Endocrinology*. 2012;153(5):2267-2276.
30. Smith AR, Macfarlane S, Furrie E, et al. Microbiological and immunological effects of enteral feeding on the upper gastrointestinal tract. *J Med Microbiol*. 2011;60(pt 3):359-365.
31. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr*. 2003;27(5):355-373.
32. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
33. Benya R, Mobarhan S. Enteral alimentation: administration and complications. *J Am Coll Nutr*. 1991;10(3):209-219.
34. Cabre E, Gassull MA. Complications of enteral feeding. *Nutrition*. 1993;9(1):1-9.
35. Ciocon JO, Silverstone FA, Graver LM, Foley CJ. Tube feedings in elderly patients: indications, benefits, and complications. *Arch Intern Med*. 1988;148(2):429-433.
36. Bohnker BK, Artman LE, Hoskins WJ. Intranasal retraction of nasogastric feeding tube: case report and suggestion for design modification. *JPEN J Parenter Enteral Nutr*. 1985;9(1):53-54.