Use of a concentrated enteral nutrition solution to increase calorie delivery to critically ill patients: a randomized, double-blind, clinical trial[1–3]

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ABSTRACT

Background: Critically ill patients typically receive ~60% of estimated calorie requirements.

Objectives: We aimed to determine whether the substitution of a 1.5-kcal/mL enteral nutrition solution for a 1.0-kcal/mL solution resulted in greater calorie delivery to critically ill patients and establish the feasibility of conducting a multicenter, double-blind, randomized trial to evaluate the effect of an increased calorie delivery on clinical outcomes.

Design: A prospective, randomized, double-blind, parallel-group, multicenter study was conducted in 5 Australian intensive care units. One hundred twelve mechanically ventilated patients expected to receive enteral nutrition for ≥2 d were randomly assigned to receive 1.5 (n = 57) or 1.0 (n = 55) kcal/mL enteral nutrition solution at a rate of 1 mL/kg ideal body weight per hour for 10 d. Protein and fiber contents in the 2 solutions were equivalent.

Results: The 2 groups had similar baseline characteristics (1.5 compared with 1.0 kcal/mL). The mean (±SD) age was 56.4 ± 16.8 compared with 56.5 ± 16.1 y, 74% compared with 75% were men, and the Acute Physiology and Chronic Health Evaluation II score was 23 ± 9.1 compared with 22 ± 8.9. The groups received similar volumes of enteral nutrition solution [1221 mL/d (95% CI: 1120, 1322 mL/d) compared with 1259 mL/d (95% CI: 1143, 1374 mL/d); P = 0.628], which led to a 46% increase in daily calories in the group given the 1.5-kcal/mL solution [1832 kcal/d (95% CI: 1681, 1984 kcal/d) compared with 1259 kcal/d (95% CI: 1143, 1374 kcal/d); $P < 0.001$]. The 1.5-kcal/mL solution was not associated with larger gastric residual volumes or diarrhea. In this feasibility study, there was a trend to a reduced 90-d mortality in patients given 1.5 kcal/mL [11 patients (20%) compared with 20 patients (37%); P = 0.057].

Conclusions: The substitution of a 1.0- with a 1.5-kcal/mL enteral nutrition solution administered at the same rate resulted in a 46% greater calorie delivery without adverse effects. The results support the conduct of a large-scale trial to evaluate the effect of increased calorie delivery on clinically important outcomes in the critically ill. This trial was registered at Australian New Zealand Clinical Trials (http://www.anzctr.org.au/) as ACTRN 12611000793910. *Am J Clin Nutr* 2014;100:616–25.

INTRODUCTION

The optimal calorie delivery for critically ill patients is unclear. It is widely believed that calorie delivery should approximate energy expenditure; however, the direct measurement of energy expenditure is rarely performed in routine clinical practice because it is difficult and impractical. The calorie requirement is usually estimated by using a variety of predictive equations, which are believed to approximate energy expenditure, with ~25–30 kcal · kg^{-1} · d^{-1} generally recommended. There are 2 major difficulties in this approach. First, it has been universally impossible to consistently deliver this amount of calories enterally (1–4). Second, although such an approach is both logical and plausible, the evidence to support the concept that matching energy expenditure with calorie delivery improves clinical outcomes has been limited to observational studies and small, randomized, controlled trials (4, 5). Although it is logical that energy delivery should match energy consumption (6), the benefits of such matching remain to be confirmed by a robust, high-quality clinical trial.

Enteral calorie delivery during critical illness has frequently and consistently been shown to provide substantially less than the full-recommended calorie requirement (3, 4, 7), mainly because of gastrointestinal dysmotility, particularly delayed gastric emptying (8), as well as fasting for procedures, surgery, and radiology (9). In an attempt to increase calorie delivery, many strategies have been tried with limited success, including promotility drugs (10, 11), small intestinal catheters (12), aggressive nutrition protocols (7), and supplemental intravenous nutrition (13). Thus, there is a sizable and well-established dissociation

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[2] Supported by the Royal Adelaide Hospital and the Australian and New Zealand College of Anaesthetists. Provision and blinding of the study feed and importation and delivery to the sites was provided by Fresenius Kabi (Germany).

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between the recommended calorie requirement and calories actually delivered. Concentrated formulae have been used frequently in clinical practice (14), mainly to provide calories while limiting fluid-volume administration; however, the safety and efficacy of the administration of a concentrated formula at a higher delivery rate to deliver 100% calorie goals has not been reported to our knowledge.

The primary aim of this study was to determine whether the substitution of a 1.0-kcal/mL enteral nutrition solution with a 1.5-kcal/mL solution delivered at the same rate resulted in the delivery of more calories to critically ill patients over the first 10 d of their enteral nutrition therapy. A secondary aim was to provide data to inform the design of a large-scale, multicenter double-blind, randomized, controlled trial to investigate whether additional enteral calorie delivery to critically ill adults affects clinically important outcomes by *1*) establishing that the intervention could be blinded, *2*) ensuring that the intervention could be safely delivered, *3*) determining event rates of various outcomes for the selected patient population, *4*) determining the recruitment rate, and *5*) determining the size of the treatment effect for the phase III primary outcome of interest (90-d mortality).

SUBJECTS AND METHODS

Setting

This study was conducted in 5 Australian university-affiliated, tertiary-referral, intensive care units (ICUs).

Patients

Patients aged ≥18 y who were undergoing invasive mechanical ventilation and expected to receive enteral nutrition for ≥2 d were randomly assigned to receive either a 1.5- or 1.0-kcal/mL enteral nutrition solution. Patients were excluded if they had already received >12 h enteral or parenteral nutrition during their ICU stay or for whom the study goal rate was contraindicated (eg, requirement for fluid restriction), or there was a requirement for a specific enteral nutrition solution (as determined by the treating clinician). Eligible patients were randomly assigned in a 1:1 ratio by using a permuted block method with variable block sizes stratified by site. Allocation concealment was maintained by using a centralized, Web-based randomization schedule accessible 24 h a day.

Patients were recruited between 23 January and 4 May 2013, and the study was carried out in accordance with the Helsinki Declaration of 1975 as revised in 1983. All participating institutional ethics committees approved the study and allowed delayed consent to be sought from either the next of kin or the patient. [Australian and New Zealand Clinical Trials Registry (http://www.anzctr.org.au/); ACTRN 12611000793910].

Study design

This was a multicenter, randomized, controlled, parallel-group, clinical feasibility trial. Patients, clinicians, and all study personnel were blinded to caloric contents of study enteral nutrition solutions.

Intervention

The blinded enteral nutrition solutions were supplied by Fresenius Kabi in identical 1-L bags, which differed only in terms of the caloric concentration (Fresubin 2250 Complete 1.5 kcal/mL compared with Fresubin 1000 Complete 1.0 kcal/mL; Fresenius Kabi Deutschland GmbH) (**Table 1**). This difference in the caloric concentration was shared between fat (0.058 compared with 0.027 g/mL) and carbohydrate (0.18 compared with 0.125 g/mL). Protein and fiber contents in the study solutions were similar at 0.056 compared with 0.055 g/mL and 0.015 compared with 0.02 g/mL for the 1.5- and 1.0-kcal/mL solutions, respectively. The 2 study interventions were clinically indistinguishable in color and packaging. The effectiveness of the blinding was confirmed in a formal bedside study at participating sites. In addition, to confirm the successful delivery of allocated enteral nutrition solutions, an independent analysis of the osmolality of the 1.5-kcal/mL (430 mOsm/kg H_2O) and 1.00-kcal/mL (360 mOsm/kg H_2O) solutions was obtained for a random sample of 261 study bags by using freezing point depression osmometry.

The study enteral nutrition was delivered at a goal rate of 1 mL · kg ideal body weight $(IBW)^{-1}$ · h^{-1} in both groups. IBW was calculated from measured height as follows (8):

$$\text{IBWfor men} = [\text{height(cm)} - 152.4] \times 0.9 + 50 \quad (1)$$

$$\text{IBWwomen} = [\text{height(cm)} - 152.4] \times 0.9 + 45.5 \quad (2)$$

Patients received study enteral nutrition for the duration of their ICU stay up to a maximum of 10 d unless enteral nutrition was ceased earlier. To reduce risk of potential overnutrition (15–17), the maximum goal rate was 100 mL/h for all patients; and at the discretion of treating clinicians, study enteral nutrition could be ceased if the goal rate was achieved for 5 consecutive days. Patients for whom consent to continue the study intervention was withdrawn were analyzed according to the intention-to-treat principle unless consent for data collection was refused.

Other than the goal rate, the duration and method of enteral nutrition delivery were at the discretion of the treating clinician according to the usual unit nutrition protocols, including the commencement rate, increments, use of promotility drugs, and small-intestinal feeding tubes. It was recommended that the goal rate be achieved within 48 h of the commencement of enteral nutrition. If supplemental parenteral nutrition was deemed necessary (eg, enteral nutrition intolerance), it was assumed that patients were receiving a 1.25-kcal/mL enteral nutrition solution to calculate the total calorie delivery and determine the amount of parenteral nutrition to administer. Stool samples were obtained from all patients with diarrhea during the intervention period and screened for infectious causes and *Clostridium difficile* toxin. Diarrhea was defined as ≥4 loose-bowel actions within a 24-h period or the use of a fecal management system for diarrhea control.

Blood glucose management was standardized, with the aim of a blood glucose concentration ≤10 mmol/L. Blood glucose concentrations ≤2.2 mmol/L were defined as a serious adverse event.

Data collection

Baseline data included patient demographics (age, sex, and ideal and actual weights); ICU admission diagnosis, category (elective or emergency surgical, medical), and Acute Physiology and Chronic Health Evaluation II score; chronic comorbidities

TABLE 1
Composition of the enteral nutrition solutions[1]

	1.0 kcal/mL	1.5 kcal/mL
Nutritional composition (/100 mL)		
Energy (kcal)	100	150
Protein (g)	5.5	5.6
Carbohydrate (g)	12.5	18
Sugars (g)	1.1	1.2
Lactose (g)	≤0.04	≤0.03
Fat (g)	2.7	5.8
SFAs (g)	0.23	0.5
MUFAs (g)	1.73	3.7
PUFAs (g)	0.74	1.6
EPA and DHA (g)	0.05	0.03
Fiber (g)	2	1.5
Water (mL)	83	76
Osmolarity (mOsm/L)	300	325
Osmolality (mOsm/kg H_2O)	360	430
Minerals and trace elements (/100 mL)		
Sodium [mg (mmol)]	153 (6.7)	100 (4.3)
Potassium [mg (mmol)]	213 (5.4)	207 (5.3)
Chloride [mg (mmol)]	153 (4.3)	153 (4.3)
Calcium [mg (mmol)]	85 (2.1)	67 (1.7)
Phosphorus [mg (mmol)]	66 (2.1)	53 (1.7)
Magnesium [mg (mmol)]	35 (1.4)	24 (1)
Iron (mg)	2	1.33
Zinc (mg)	1.5	1.2
Copper (mg)	0.2	0.13
Manganese (mg)	0.4	0.27
Iodide (μg)	2.0	13.3
Chromium (μg)	10	6.7
Molybdenum (μg)	15	10
Fluoride (mg)	0.2	0.13
Selenium (μg)	10	6.7
Vitamins and other nutrients (/100 mL)		
Vitamin A (μg)	105	70
β-Carotene (mg)	0.2	0.13
Vitamin D (μg)	1.5	1
Vitamin E (mg)	2	3
Vitamin K (μg)	10	6.67
Thiamine (mg)	0.2	0.13
Riboflavin (mg)	0.26	0.17
Niacin (mg)	2.4	1.6
Vitamin B-6 (mg)	0.24	0.16
Vitamin B-12 (μg)	0.4	0.27
Pantothenic acid (mg)	0.7	0.47
Biotin (μg)	7.5	5
Folic acid	40	26.7
Vitamin C (mg)	10	6.67
Choline (mg)	55	36.7
Typical fatty acid profile (g/mL)		
14 (myristic acid)	—	0.009
16 (palmitic acid)	0.16	0.291
16:n−7 (palmitoeic acid)	0.02	0.011
18 (stearic acid)	0.09	0.144
18:1n−9 (oleic acid)	1.95	3.486
18:2n−6 (linoleic acid)	0.56	1.101
18:3 (α-linolenic acid)	0.23	0.418
20:5n−3 (EPA)	0.03	0.029
22:6n−3 (DHA)	0.02	0.019
n−6:n−3 ratio	2:1	2.3:1
Typical amino acid profile (g/100 mL)		
Essential		
Lysine	0.46	0.44

(Continued)

(including diabetes); and a dietitian assessment of nutritional requirements. Data were collected daily for up to 14 d after randomization included: study enteral nutrition, nonstudy nutrition administration [parenteral nutrition, incidental calories (eg, 50% dextrose and propofol), intolerance to enteral nutrition (gastric residual volumes, diarrhea, and promotility agents), highest and lowest blood glucose concentrations, and insulin administration].

Outcomes

The primary outcome was the daily calorie delivery (kcal/d) from study enteral nutrition. Secondary outcomes were as follows: *1*) the daily total calorie delivery from enteral nutrition, parenteral nutrition, and incidental calories; *2*) daily enteral and total calorie delivery calculated per unit of IBW (kcal · kg^{-1} · d^{-1}); *3*) ICU and hospital length of stay; *4*) ventilator-free days (defined as the number of days between successful weaning from mechanical ventilation and day 28 after study enrollment in patients who survived to 28 d); and *5*) ICU, hospital, and 28- and 90-d mortality.

Statistical analysis

The sample size of 112 patients for the feasibility trial was based on data from previous studies by our group and other nutrition studies conducted in Australia and New Zealand (7). With the assumption of a mean (±SD) daily calorie delivery with enteral nutrition of 1300 ± 400 kcal/d in the 1.0-kcal/mL (usual treatment) group, the expectation of at least a 20% increase in calorie delivery with the higher-concentration 1.5-kcal/mL solution, and with the use of a 2-group *t* test at 5% significance and 80% power, the estimated minimum required sample size was 38 patients/ group (ie, 76 patients in total). To allow for more-reliable estimates of the recruitment rate and baseline mortality and compensate for some recruited patients receiving less than the anticipated 2 d of enteral nutrition, 112 patients (56 patients/ group) were enrolled.

All analyses were conducted according to the intention-to-treat principle. No stopping rules or interim analyses were planned. For missing data, the number of available observations was reported, and missing values were not imputed. Continuous variables are reported as means (±SDs) or median (IQRs). Proportions are reported as percentages with 95% CIs. Differences between groups were analyzed, as appropriate, by using Student's *t* test, Wilcoxon's rank tests or Mann-Whitney *U* tests for continuous variables and Pearson's chi-square or Fisher's exact test for categorical variables. The overall calorie delivery was calculated as total intake divided by the number of days fed and expressed as intake per 24 h Daily intakes were analyzed in linear mixed-effects models with fixed effects for group, day, and the group by day interaction with a heterogeneous first-order autoregressive covariance structure for repeated measurements.

Ventilator-free days to day 28 were calculated as previously described (18). Patients who died before day 28 were assigned zero ventilator-free days. Absolute risk differences with 95% CIs for 90-d all-cause mortality are reported. The survival time from random assignment to day 90 was compared using a Kaplan-Meier analysis and the log-rank test. The length of stay was analyzed by using log rank tests with death considered a

TABLE 1 (*Continued*)

	1.0 kcal/mL	1.5 kcal/mL
Threonine	0.26	0.26
Methionine	0.16	0.13
Phenalanine	0.29	0.32
Tryptophan	0.08	0.08
Valine	0.40	0.39
Leucine	0.55	0.56
Isoleucine	0.32	0.33
Conditionally essential	—	—
Tyrosine	0.3	0.28
Cysteine	0.03	0.05
Taurine	—	—
Histidine	0.16	0.17
Arginine	0.20	0.34
Nonessential		
Glycine	0.10	0.21
Alanine	0.18	0.24
Proline	0.55	0.48
Serine	0.34	0.36
Glutamine	0.52	0.52
Glutamic acid	—	0.73
Glutamine and glutamic acid	0.68	—
Aspartic acid and asparagine	0.41	0.58
Typical carbohydrate profile (g/100 mL)		
Glucose	0.2	0.2
Fructose	0.08	0.03
Maltose	0.72	0.93
Sucrose	0.06	0.04
Lactose	≤0.04	≤0.03
Polysaccharides and oligosaccharides	11.5	17.4
Starch	—	0.2

[1] Formulae: 1 kcal/mL (Fresubin 1000 Complete tube feed; Fresenius Kabi Deutschland GmbH); 1.5 kcal/mL (Fresubin 2250 Complete tube feed; Fresenius Kabi Deutschland GmbH).

competing event that precluded discharge. Deaths were censored at values after the last observed discharge for ICU and hospital stays.

Statistical analyses were performed with IBM SPSS Statistics software (version 20, 2011; IBM Inc). Statistical significance was defined as $P < 0.05$.

RESULTS

Study patients

Of 415 patients assessed for eligibility, 112 patients were enrolled (1.5 patients per site per week) and randomly assigned to receive 1.5 kcal/mL (57 patients) or 1.0 kcal/mL (55 patients) enteral nutrition solution (**Figure 1**). All patients were assessed for the primary outcome. One patient in the 1.5-kcal/mL group requested to be withdrawn from the study on day 4, and one patient in the 1.0-kcal/mL group was lost to follow-up by day 90.

Baseline characteristics

The mean age was 56.4 ± 16.4 y, and the majority (74%) of patients were men (74%) with an Acute Physiology and Chronic Health Evaluation II score of 23 ± 9.0. Seventy-one percent of patients had a medical condition, and 14% of patients had an emergency surgical condition. No differences in baseline characteristics were observed between the 2 groups (**Table 2**). The time from ICU admission to random assignment was not different (21 h for both). A dietitian assessment of calorie requirements was performed on 88 patients (79%), most commonly by using a fixed prescription of 20–25 kcal/kg in 43 patients (48%) or Schofield's equation (with or without a stress factor) in 40 patients (45%). Dietitian-estimated daily calorie requirements for the 1.5- and 1.0-kcal/mL groups were 1909± 312 and 1840 ± 318 kcal/d, respectively ($P = 0.306$).

Calorie delivery

The number of days study enteral nutrition was delivered over the 10-d intervention period was 7 d (4–9 d) and 4 d (3–9 d) for the 1.5- and 1.0-kcal/mL groups, respectively ($P = 0.245$). On day 10, 15 patients (27%) and 14 patients (25%) were still receiving study enteral nutrition in the 1.5- and 1.0-kcal/mL groups respectively. Between days 11 and 14, 33 patients continued to receive enteral nutrition [17 patients (30%) in the 1.5-kcal/mL group; 16 patients (29%) in the 1.0-kcal/mL group].

The daily volume of study enteral nutrition delivered in the 2 groups was similar [1.5 compared with 1.0 kcal/mL:1221 mL (95% CI: 1120, 1322 mL) compared with 1259 mL (95% CI: 1143, 1374) mL, respectively; $P = 0.628$] (**Table 3**). Overall, there were a total of 364 feeding days in the 1.5-kcal/mL group, and a daily goal rate (on the basis of 1 mL · kg IBW^{-1} · h^{-1}) was achieved on 136 d (37%). In the 1.0-kcal/mL group, there were a total of 311 feeding days, and daily goal rate was achieved on 137 d (44%). The number of patients who achieved a goal rate on ≥1 d was 45 (82% of patients) and 47 (85% of patients) in the 1.5- and 1.0-kcal/mL groups, respectively. The time to achieve the goal rate was the same for both groups at 2 d (1–3 d). Reasons for not achieving the goal rate on any day were similar between the 2 groups and included a planned endotracheal extubation or procedure outside the ICU (63% of patients), vomiting or regurgitation (22% of patients), large gastric residual volumes (26% of patients) and enteral tube removal or blockage (16% of patients).

The administration of the 1.5-kcal/mL enteral nutrition formula resulted in a 46% greater daily calorie delivery [1832 kcal (95% CI: 1681, 1984 kcal) compared with 1259 kcal (95% CI: 1143, 1374 kcal); $P < 0.001$) (**Figure 2**). The proportion of estimated daily calorie requirements (on the basis of the dietitian's assessment) delivered by the study enteral nutrition was 102% and 72% for the 1.5- and 1.0-kcal/mL groups, respectively ($P < 0.001$). The number of patients who achieved their estimated daily caloric requirements on one or more study feeding days was 40 patients (89%) and 7 patients (16%) in the 1.5- and 1.0-kcal/mL groups, respectively (**Figure 3**). Protein delivery was the same for both groups (Table 3), with 75% of that estimated by the dietitian in the 1.5-kcal/mL group and 79% of that estimated in the 1.0-kcal/mL group.

Enteral nutrition calories delivered per kilogram of IBW were substantially greater in the group given 1.5 kcal/mL than for the group who received 1.0 kcal/mL (27.3 ± 7.4 compared with 19.0 ± 6.0 kcal · kg^{-1} · d^{-1}, respectively; $P < 0.001$) (Table 3). Total daily calorie delivery from study solution, parenteral nutrition and other calorie sources combined was also higher for the 1.5-kcal/mL group ($P < 0.001$).

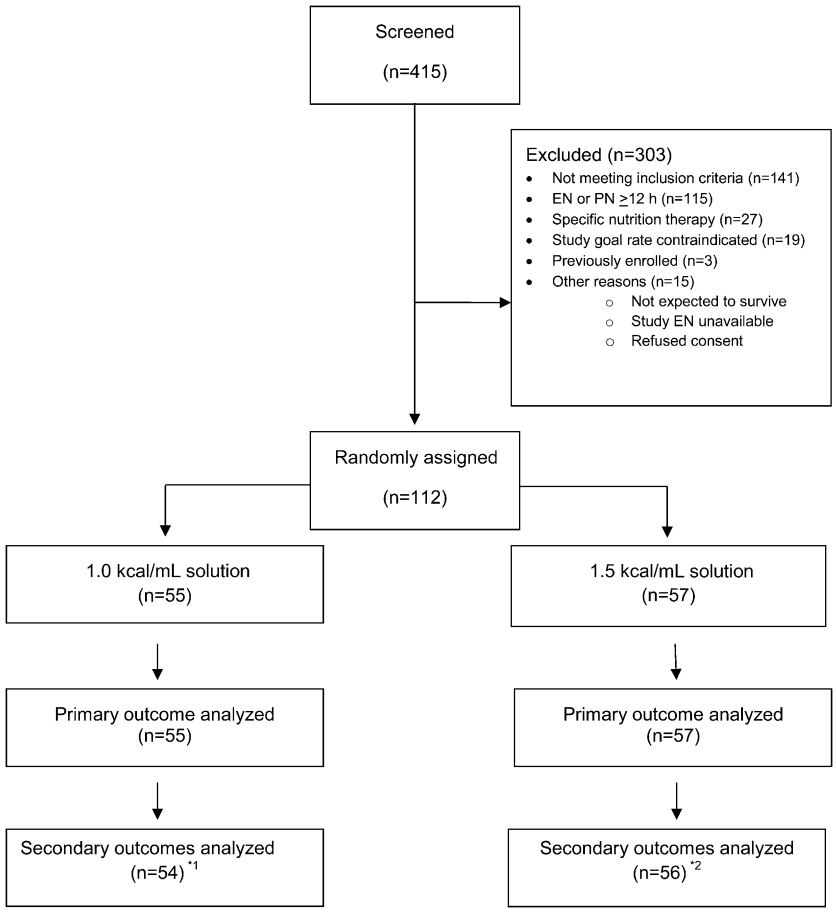

FIGURE 1. Patient flow diagram. Numbers of patients enrolled in the study, randomly assigned to receive 1.5- or 1.0-kcal/mL enteral nutrition solution, and included in the final analysis. *1 $n = 1$ lost to follow-up and excluded from the secondary outcome analysis: 90-d mortality; *2 $n = 1$ withdrawal of consent on study day 4. (Included in the intention-to-treat analysis of the primary endpoint, but data were not available beyond study day 4 for secondary outcomes.) EN, enteral nutrition; PN, parenteral nutrition.

An independent analysis of the osmolality of a random sample of study bags confirmed the delivery of the allocated solutions [1.5 kcal/mL (n = 147); median (IQR): 496 mOsm/kg H_2O (488–507 mOsm/kg H_2O) compared with 1.0 kcal/mL (n = 114); 383 mOsm/kg H_2O (377–388 mOsm/kg H_2O); $P < 0.001$]. The 2 blinded feeds were clinically indistinguishable ($P = 1.0$; Fisher's exact test).

Clinical outcomes

At 90 d, 11 patients (20%) in the 1.5-kcal/mL group and 20 patients (37%) in the 1.0-kcal/mL group had died ($P = 0.057$; Fisher's exact test) (**Table 4**). The absolute risk reduction in mortality for the 1.5-kcal group compared with the 1.0-kcal/mL group was 17% (95% CI: 0.6, 33). The survival time from random assignment to day 90 tended to be longer in patients who received the 1.5-kcal/mL formula ($P = 0.057$) (**Figure 4**), and there was no difference in the proximate cause of death ($P = 0.882$) (Table 3). ICU, hospital, and 28-d mortality were not different between the 2 treatment groups. One patient in the 1.5-kcal/mL group and 6 patients in the 1.0-kcal/mL group died after hospital discharge. The number of mechanical ventilation-free days to day 28, ICU, and hospital length of stay (for survivors only) and destination at hospital discharge were also not different (Table 3).

Complications of therapy

Enteral nutrition was never ceased because of treating clinician concerns of overnutrition. Supplemental parenteral nutrition was administered to 4 patients (1.5 kcal/mL, 2 patients; 1.0 kcal/mL, 2 patients). There was no difference between groups in terms of gastrointestinal intolerance (large gastric residual volumes, use of promotility or laxative agents, and diarrhea) (Table 3). Two of 40 patients with diarrhea had *Clostridium difficile* toxin detected. The increased calorie delivery in the 1.5-kcal/mL group was associated with a trend to a slightly higher peak blood glucose concentration over the 10-d study period (1.5 kcal/mL; 12.4 ± 3.9 mmol/L compared with 1.0 kcal/mL; 12.0 ± 3.9 mmol/L; $P = 0.056$); but the number of patients who required insulin on ≥1 d was no greater in the 1.5-kcal/mL group [1.5 kcal/mL (54%) compared with1.0 kcal/mL (42%); $P = 0.183$]. No episodes of hypoglycemia (≤2.2 mmol/L) were reported.

DISCUSSION

In this multicenter, randomized, double-blind study, the administration of a 1.5-kcal/mL enteral nutrition formula resulted in a near 50% increase in calorie delivery compared with a 1.0-kcal/mL formula in mechanically ventilated patients. To our knowledge,

TABLE 2
Baseline characteristics of the study patients[1]

Variable	1.5 kcal/mL (n = 57)	1.0 kcal/mL (n = 55)	P[2]
Age (y)	56.4 ± 16.8[3]	56.5 ± 16.1	0.964
M	42 ± 74	41 ± 75	0.917
APACHE II score	23 ± 9.1	22 ± 8.9	0.560
APACHE III diagnostic code [n (%)]			0.442
Cardiovascular	12 (21)	8 (15)	
Respiratory	9 (16)	12 (22)	
Gastrointestinal	4 (7)	3 (6)	
Neurological	8 (14)	15 (27)	
Sepsis	7 (12)	4 (7)	
Trauma	11 (19)	6 (11)	
Other	6 (11)	7 (13)	
ICU admission category [n (%)]			0.095
Emergency operative	11 (19)	5 (9)	
Emergency nonoperative	35 (61)	44 (80)	
Elective operative	11 (19)	6 (11)	
Past medical history diabetes mellitus [n (%)]	13 (23)	13 (24)	0.917
BMI (kg/m^2)	27.8 ± 7.9	26.2 ± 6.4	0.241
Actual weight[4] (kg)	83 ± 23.2	77 ± 16.4	0.118
IBW[5] (kg)	67 ± 9.2	67 ± 9.1	0.675
Energy requirements[6] (kcal/d)	1909 ± 312	1840 ± 318	0.306
Protein requirements[6] (g/d)	91 ± 16	87 ± 12	0.178
Time from ICU admission to random assignment[7] (h)	21 (13–36)	21 (13–41)	0.836
SI tube [n (%)]	4 (7)	1 (2)	0.364

[1] APACHE, Acute Physiology and Chronic Health Evaluation; IBW, ideal body weight; ICU, intensive care unit; SI, small intestinal.

[2] A chi-square test was used to determine differences in baseline categorical variables, and a Student's t test was used for all continuous variables except time from ICU admission to random assignment (Mann-Whitney U test).

[3] Mean ± SD (all such values).

[4] Actual weight was measured or estimated if not possible.

[5] IBW was calculated by using the measured height and the following formulae: IBW for men = [height (cm) – 152.4) × 0.9 + 50; IBW for women = [height (cm) – 152.4] × 0.9 + 45.5.

[6] Energy and protein requirements were estimated by the dietitians at the site at study entry.

[7] Values are medians; IQRs in parentheses.

this is the first study in this patient population to describe the use of a concentrated enteral nutrition formula to deliver more calories to patients in a double-blind fashion. Furthermore, in this feasibility study, we have confirmed the effectiveness of the blinding process, identified a cohort of critically ill patients whose outcome may be improved by increased calorie delivery (ie, longer-stay, mechanically ventilated patients with a 90-d mortality ~28%), and established the potential recruitment rate and treatment-effect size necessary for sample-size calculations for a large-scale trial.

Previous studies designed to deliver more calories to critically ill patients have used techniques including nutrition protocols (7, 19–21) and small-intestinal feeding catheters (12, 22, 23). Both strategies have had small effects on calorie delivery. The administration of promotility drugs or supplemental parenteral nutrition has resulted in a greater calorie delivery, but it is unclear if this method offers advantages in terms of clinically meaningful outcomes (10, 13, 24, 25). It is also possible that potential benefits from an increased calorie delivery may be outweighed by adverse effects from the method used. In the EDEN study, a difference in enteral calorie delivery was achieved, but in the full-feeding group, only 1300 kcal/d were delivered, which was a similar amount of calories as was given to our 1.0-kcal/mL group (1259 kcal/d; 19.0 kcal · kg^{-1} · d^{-1}) (26). In contrast, we have shown that >1800 kcal/d (27 kcal · kg IBW^{-1} · d^{-1}) was delivered to a heterogeneous population of critically ill patients by using a 1.5-kcal/mL enteral nutrition solution. Although the EDEN study results suggested there was no difference in clinical outcomes when the administration of 1300 compared with 400 kcal/d was compared for the first week of ICU nutrition therapy, it remains a plausible hypothesis that the delivery of 1800 kcal/d (which is closer to expected requirements) could be associated with improved clinical outcomes.

The use of concentrated enteral nutrition solutions has become more popular in recent years in ICU patients (14). Concentrated solutions may be prescribed when a patient is intolerant to enteral nutrition on the assumption that the delivery of lower volume, greater caloric content solutions may be better tolerated to allow increased calorie delivery (14). This premise has never been proven. Conversely, it is possible that concentrated solutions may be less-well tolerated because of the formula being emptied more slowly from the stomach into the small intestine, leading to increased gastric residual volumes (27). There have also been concerns that concentrated enteral nutrition solutions may be associated with increased osmotic diarrhea (28); although studies have refuted this association (29). The effects of concentrated solutions on clinical outcomes, including mortality, have also been questioned in an observational study of critically ill trauma

TABLE 3
Nutrition data[1]

Variable	1.5 kcal/mL (n = 57)	1.0 kcal/mL (n = 55)	P[2]
Calories (overall/24-h study period)			
Study EN (kcal)	1832 ± 381[3]	1259 ± 428	< 0.001
Study EN/kg (kcal/kg)	27.3 ± 7.4	19.0 ± 6.0	< 0.001
Study EN − GRV (kcal)	1699 ± 682	1194 ± 454	<0.001
EN + PN + other (kcal)	2040 ± 578	1504 ± 573	< 0.001
(EN + PN + other) − GRV (kcal)	1617 ± 740	1291 ± 623	0.014
Protein (overall/24-h study period)			
Study EN (g)	68 ± 21	69 ± 24	0.847
Study EN/kg (g/kg)	1.02 ± 0.28	1.05 ± 0.33	0.618
EN + PN + other (g)	70 ± 20	74 ± 30	0.395
Volume (overall/24-h study period)			
Study EN (mL)	1221 ± 381	1259 ± 428	0.628
Gastric residual volume (mL)			
Total volume/24 h	166 (48–324)[4]	80 (37–261)	0.260
Returned/24 h	126 (41–262)	70 (29–145)	0.050
Largest individual measurement	200 (50–360)	105 (40–278)	0.129
Regurgitation (over study period) [n (%)]	12 (21)	13 (24)	0.743
Promotility drugs (over study period) [n (%)]	28 (49)	25 (46)	0.697
Laxative drugs (over study period) [n (%)]	36 (63)	29 (53)	0.263
Fecal management system [n (%)] (over study period)	8 (14)	13 (24)	0.193
Diarrhea [n (%)]	20 (35)	20 (36)	0.888
Day first had diarrhea	5 (3–8)	4 (2–6)	0.369
Insulin dose, mean dose/d (IU)	55 (22–131)	43 (24–67)	0.308
Blood glucose concentration ≤2.2 mmol/L [n (%)]	0 (0)	0 (0)	—

[1] In variables, "other" refers to incidental calorie intake provided by propofol and dextrose infusions. EN, enteral nutrition; GRV, gastric residual volume; PN, parenteral nutrition.

[2] Differences between 1.5- and 1.0-kcal/mL enteral nutrition solutions were assessed by using a Student's t test for all continuous variables except for measures of gastric residual volume, the day the patient first had diarrhea, and insulin dose (Mann-Whitney U test), and a chi-square test was used for categorical variables.

[3] Mean ± SD (all such values).

[4] Median; IQR in parentheses (all such values).

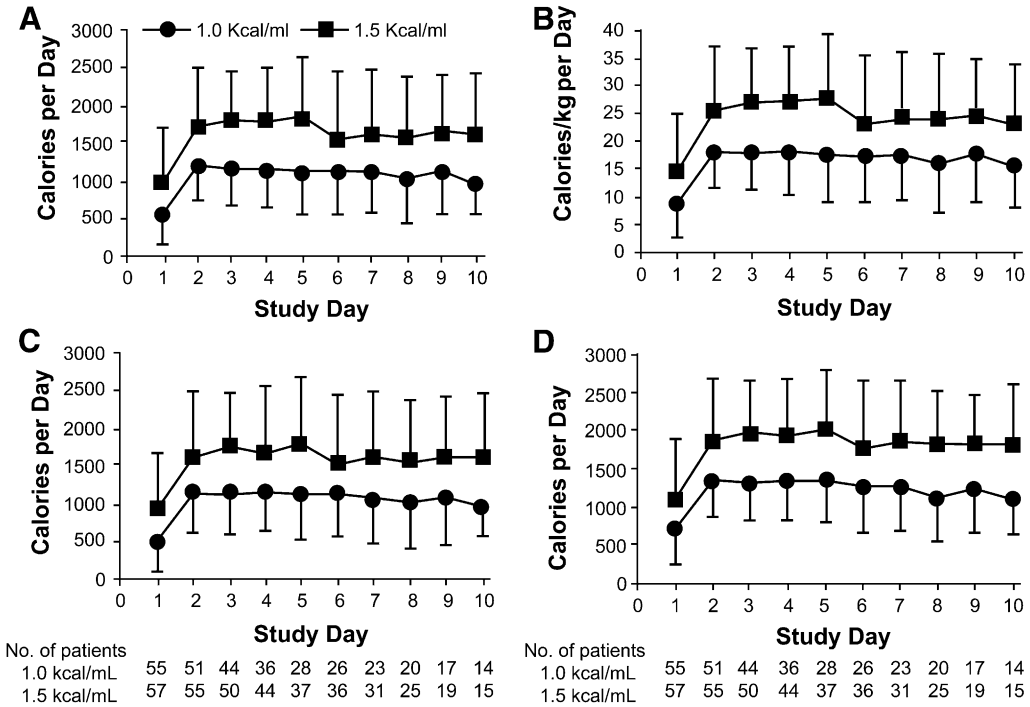

FIGURE 2. Mean (±SD) daily calorie delivery over the 10-d study-intervention period. A: Calories provided by the study enteral solution (kcal). B: Calories per kilogram of ideal body weight provided by the study enteral solution (kcal/kg). C: Calories provided by study enteral solution (kcal) minus the gastric residual volume (kcal). D: Total calories provided by the study enteral solution (kcal) plus intravenous nutrition, propofol, and glucose infusions (kcal).

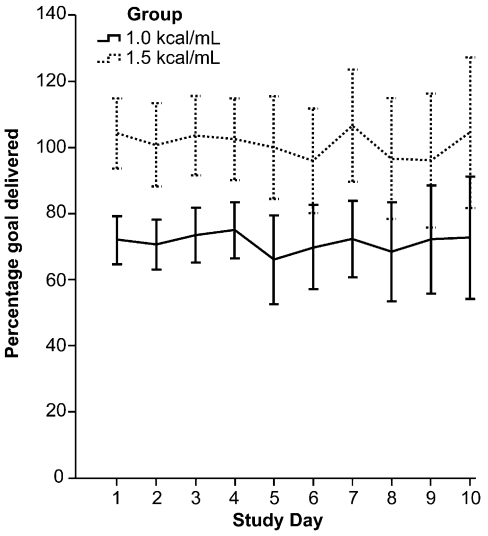

FIGURE 3. Mean (±SD) estimated goal calories delivered per day from 1.5- and 1.0-kcal/mL enteral nutrition solutions. Estimated daily caloric requirements were based on the dietitian's assessment at study entry [available for 88 patients (79%)].

and surgical patients (22). This current study has shown that the use of a concentrated solution is both effective and safe in delivering more calories. There was no difference in enteral intolerance (gastric residual volumes, regurgitation, use of promotility drugs, or diarrhea) or glucose control between the 2 enteral nutrition solutions. Although our study was not powered to detect differences in adverse effects, the sample size was sufficient to observe useful numbers of events for these important potential complications. The results also provide information to determine the sample size for an adequately powered, future, large-scale study for these outcomes.

To our knowledge, this is the first enteral nutrition study to successfully blind the study intervention in this patient population (26, 30). The concealment of the intervention was important to prevent inadvertent bias (31). In previous studies, blinding of the intervention has not been undertaken, which raises concerns about reported differences in outcomes, particularly when outcomes were subject to an ascertainment bias (eg, nosocomial infections and functional outcomes) (6, 24, 25). We were able to overcome the substantial logistical problems of designing a double-blind enteral nutrition study by using 2 commercially available enteral nutrition solutions that were similar in color, indistinguishable at the bedside, and delivered at the same flow rate and volume to both study groups.

This feasibility study had several limitations. The study was not powered to detect a mortality difference. However, as noted by the Australian and New Zealand Clinical Trials Group consensus panel meeting on endpoints for phase II trials, a signal for improved survival supports the conduct of a phase III trial with 90-d survival as the primary outcome of interest (32). Nevertheless, note that there were less deaths at 90 d numerically in the group who received more calories. If calorie delivery affects outcomes, it is likely to be late, possibly after ICU discharge. Our findings suggest that the effects of nutritional interventions on post–ICU-discharge mortality should be rigorously sought.

Another limitation of our study is that we did not assess functional outcomes. However, there was no difference between the 2 groups in the destination after hospital discharge, which could be considered a crude measure of the functional outcome.

TABLE 4
Clinical outcome data[1]

Variable	1.5 kcal/mL (n = 57)	1.0 kcal/mL (n = 55)	P
Number of ventilator-free days to day 28	21.1 (3.4–25.0)[2]	18.7 (0–25.6)	0.638
Duration of ICU stay (d)[3]	9.6 (5.9–22.6)	11.8 (6.9–22.8)	0.408
Duration of hospital stay (d)	34.5 (16.9–83.6)	30.6 (15.2–undefined)[4]	0.700
Destination at hospital discharge [n (%)]			
Home	21 (48)	19 (50)	0.953
Rehabilitation facility	10 (23)	7 (18)	
Another acute care hospital	9 (21)	9 (24)	
Chronic care facility	4 (9)	3 (8)	
Mortality [n (%)]			
ICU mortality	6 (11)	9 (16)	0.419
Hospital mortality [n (%)]	10 (19)	14 (27)	0.357
28-d mortality [n (%)]	11 (20)	18 (33)	0.135
90-d mortality [n (%)]	11 (20)	20 (37)	0.057
Duration of survival (d)	77 ± 4.5[5]	68 ± 5.6	0.057
Proximate cause of death [n (%)]			
Cardiovascular	4 (36)	6 (30)	0.882
Respiratory	2 (18)	6 (30)	
Neurologic	4 (36)	7 (35)	
Other	1 (9)	1 (5)	

[1] Differences between 1.5- and 1.0-kcal/mL enteral nutrition solutions were assessed by using a Mann-Whitney U test for continuous variables, a chi-square test for categorical variables, and a Fisher's exact test for mortality. ICU, intensive care unit.

[2] Median; IQR in parentheses (all such values).

[3] ICU, intensive care unit.

[4] The IQR was undefined when >25% of patients died or were not discharged from the primary hospital.

[5] Mean ± SE (all such values).

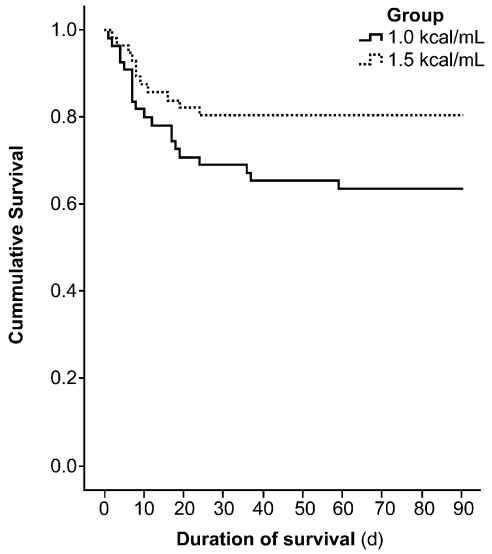

FIGURE 4. Kaplan-Meier estimates of survival time to day 90.

The National Heart, Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network group looked at functional outcomes in a subset of patients enrolled in the EDEN study and showed that there was no benefit in the administration of 1300 compared with 400 kcal/d on functional outcomes at 12 mo, albeit only 174 patients were included in this subgroup analysis (33). Future studies that investigated the effect of nutrition in this population should also include functional outcomes.

Finally, it is important to emphasize that the optimal dose of protein administration in critical illness is unclear. In this study, both groups of patients received $\sim 1\ g \cdot kg^{-1} \cdot d^{-1}$. Establishing the feasibility of delivering 2 enteral nutrition solutions with different caloric contents but the same protein contents would allow additional investigation on the isolated effects of calorie delivery. However, it should be noted that the difference in calorie delivery achieved in this study reflected a difference in carbohydrate and lipid concentrations in the 2 formulae, and the effect of the macronutrient composition on clinical outcome is an area that needs additional attention. Future clinical studies that examined the effect of enteral nutrition on clinical outcomes will need to carefully consider the calorie and protein balance.

In conclusion, the substitution of a standard 1.0-kcal/mL enteral nutrition solution with a concentrated 1.5-kcal/mL solution, administered at the same rate, resulted in an $\sim$50% increase in calorie delivery. The delivery of more calories was achieved in a blinded fashion and was also associated with a trend to improved survival. These data support the conduct of a large, multicenter, randomized, double-blind trial to determine whether the delivery of more calories by using a concentrated enteral nutrition solution can result in improved survival and functional outcomes for critically ill patients.

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The authors' responsibilities were as follows—MJC, ARD, AMD, SNO, SLP, EJR, and PJW: were management committee members and designed the research (project conception, development of overall research plan, and study oversight); MJC, ARD, AMD, KL, JLM, SNO, SLP, and EJR: formed the writing committee and were responsible for drafting the manuscript; RB, MJC, SF, SSR, and SLP: were involved in the study design, and management; other participating site investigators: conducted the research (hands-on conduct of experiments and data collection); KL and JLM: were involved in the study design, analyzed data, performed statistical analyses, and participated in the preparation of the manuscript; SLP and MJC: co-chaired the management and writing committees, had responsibility for the final content of the manuscript. Fresenius Kabi had no influence over the study protocol or the analysis or interpretation of the results. None of the authors had a conflict of interest.

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