Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial

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Summary

Background Enteral nutrition (EN) is recommended for patients in the intensive-care unit (ICU), but it does not consistently achieve nutritional goals. We assessed whether delivery of 100% of the energy target from days 4 to 8 in the ICU with EN plus supplemental parenteral nutrition (SPN) could optimise clinical outcome.

Methods This randomised controlled trial was undertaken in two centres in Switzerland. We enrolled patients on day 3 of admission to the ICU who had received less than 60% of their energy target from EN, were expected to stay for longer than 5 days, and to survive for longer than 7 days. We calculated energy targets with indirect calorimetry on day 3, or if not possible, set targets as 25 and 30 kcal per kg of ideal bodyweight a day for women and men, respectively. Patients were randomly assigned (1:1) by a computer-generated randomisation sequence to receive EN or SPN. The primary outcome was occurrence of nosocomial infection after cessation of intervention (day 8), measured until end of follow-up (day 28), analysed by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00802503.

Findings We randomly assigned 153 patients to SPN and 152 to EN. 30 patients discontinued before the study end. Mean energy delivery between day 4 and 8 was 28 kcal/kg per day (SD 5) for the SPN group (103% [SD 18%] of energy target), compared with 20 kcal/kg per day (7) for the EN group (77% [27%]). Between days 9 and 28, 41 (27%) of 153 patients in the SPN group had a nosocomial infection compared with 58 (38%) of 152 patients in the EN group (hazard ratio 0·65, 95% CI 0·43–0·97; p=0·0338), and the SPN group had a lower mean number of nosocomial infections per patient (–0·42 [–0·79 to –0·05]; p=0·0248).

Interpretation Individually optimised energy supplementation with SPN starting 4 days after ICU admission could reduce nosocomial infections and should be considered as a strategy to improve clinical outcome in patients in the ICU for whom EN is insufficient.

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Introduction

Nutritional support for patients in the intensive-care unit (ICU) is part of standard care. When the gastrointestinal tract is functioning, guidelines recommend early initiation of enteral nutrition (EN).[1–3] However, findings have shown that EN alone frequently results in insufficient energy and protein intakes[4] leading to underfeeding, which causes complications. Even in stable patients in the ICU, early initiation of EN is associated with a high incidence of gastrointestinal intolerance, and potentially serious adverse events, such as bronchoaspiration[5] with an increased risk of pneumonia.[6]

Results of meta-analyses show that parenteral nutrition (PN) is not associated with excess mortality compared with EN.[2,7] However, the optimum timing of PN initiation is controversial. We previously proposed an algorithm using the supplemental PN (SPN) approach (EN combined with PN when EN alone is insufficient),[8] which aims to optimise clinical outcome by providing patients with their full energy target from day 4 after admission to the ICU. However, the combination of PN with EN can cause overfeeding,[9] leading to increased risk of infection, metabolic disturbances such as hyperglycaemia, liver dysfunction, and extended time on mechanical ventilation. Therefore both underfeeding and overfeeding carry risks of infectious complications and can delay weaning from mechanical ventilation.

We aimed to test the hypothesis that individually optimised energy provision by SPN for 5 days after day 3 of ICU admission could improve clinical outcome in severely ill patients in the ICU for whom EN alone is insufficient.

Methods

Trial design and patients

This two-centre, randomised, controlled, intervention trial took place in the mixed medical and surgical ICUs of two tertiary care hospitals in Switzerland: Geneva University Hospital and Lausanne University Hospital. After trial approval by both institutional ethics committees, we recruited adult patients 3 days after they had been admitted to the ICU. Written informed consent was obtained from the patients or their next of kin.

Eligible patients were those who had received less than 60% of their energy target from EN at day 3 after admission to the ICU, were expected to stay for more than 5 days, expected to survive for more than 7 days, and had a functional gastrointestinal tract. We excluded those who were receiving PN, had persistent gastrointestinal dysfunction and ileus, were pregnant, refused to consent, or had been readmitted to the ICU after previous randomisation.

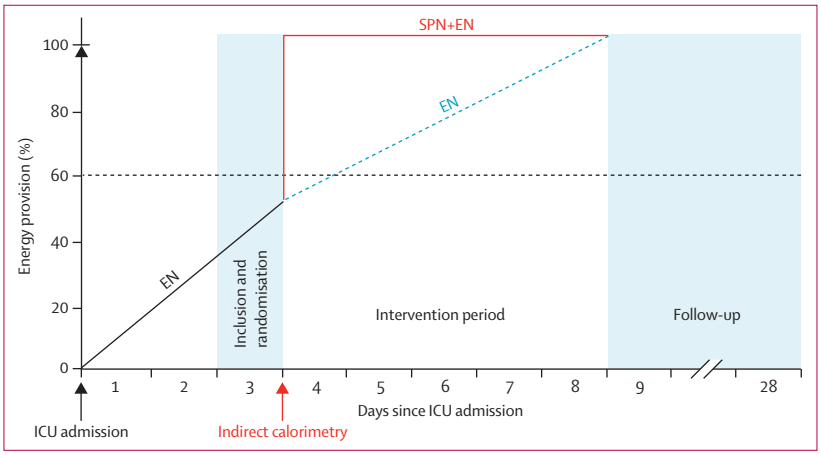

Figure 1: **Trial design**
The black solid line shows the potential progression of EN in all patients before inclusion into the trial (day 3), and the blue line shows the potential energy provision for patients remaining on EN only. The red line shows the energy delivery in patients on EN with SPN during the intervention period (days 4–8), resulting in the potential prescription of 100% of the energy target (determined by indirect calorimetry, 3 days after admission in the ICU). EN=enteral nutrition. ICU=intensive-care unit. SPN=supplemental parenteral nutrition.

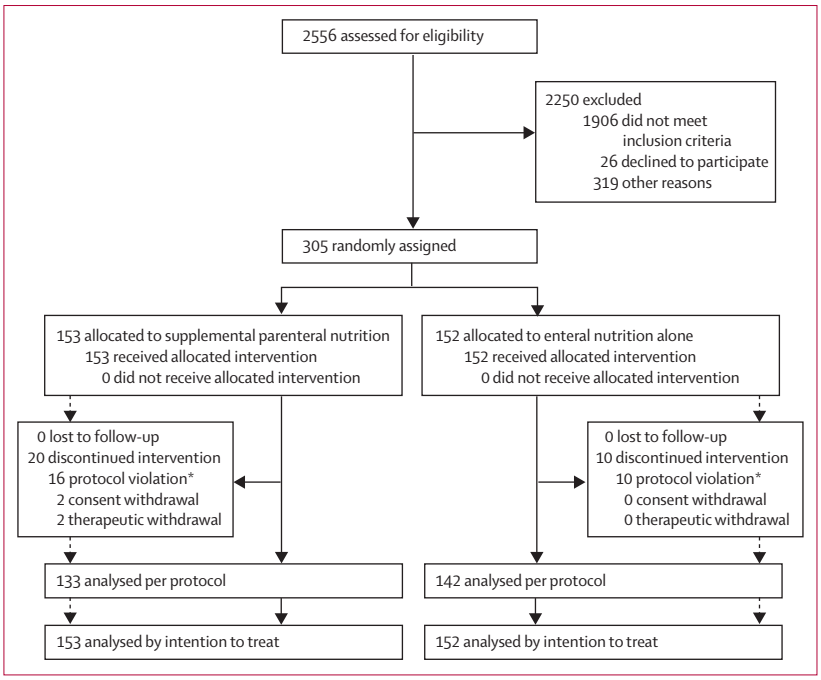

Figure 2: **Trial profile**
*We considered the protocol to be violated if the proportion of the energy target delivered by EN was more than 60% after inclusion on day 3, or if the patient stayed in the ICU for less than 5 days, or died before day 9.

Randomisation and masking

On day 3, consecutive patients were randomly assigned (1:1) to receive EN with SPN, or to continue with EN alone. The pharmacies of both hospitals generated the allocation schedule with a computer-generated randomisation sequence stratified by sex, admission category (surgery or medicine), and subsequent block size of four for SPN or EN. Allocation concealment was achieved with sequentially numbered, sealed, opaque envelopes. The daily on-duty investigator told the physician in charge of the eligible patient which treatment had been assigned. Care providers and patients were not masked; however, the investigators who established caloric goals were not directly involved in patient care. The senior site investigator from each university hospital prospectively obtained information about infectious episodes in study patients from the other centre, and was unaware of the treatment groups assigned to patients. Statisticians were masked to group allocation.

Procedures

At ICU admission (day 1) the nutritional target was set for all admitted patients at 25 kcal per kg of ideal bodyweight a day for women and 30 kcal per kg of ideal bodyweight a day for men,[1] and anamnestic bodyweight was used for patients with a body-mass index of 20 kg/m² or lower. Protein administration was set to 1·2 g per kg of ideal bodyweight a day.[1] From day 1, all patients in the ICU who were unable to eat orally were given EN (20–30 mL/h up to a maximum of 150 mL/h). EN was administered continuously by the primary care team according to routine protocols, including the following items: semi-recumbent positioning, preferred use of nasogastric tubes, and the use of prokinetic agents if necessary (gastric residual volume ≥300 mL). EN products consisted of polymeric, fibre-enriched formulas, routinely prescribed in both hospitals, containing 1·05–1·62 kcal/mL of energy (18% proteins, 29% lipids [8% medium-chain triglycerides], 53% carbohydrates).

We assessed baseline characteristics at ICU admission (day 1) for all admitted patients. We measured severity of illness with the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology II (SAPS II) scores. On day 3 of ICU admission, after randomisation took place, we used indirect calorimetry (Deltatrac II metabolic monitor, Datex-Ohmeda, Finland) to adjust the energy target to be delivered from day 4 for all study patients. On day 4, SPN was administered by central or peripheral catheter for 5 days (figure 1). PN formulas consisted of 0·62–1·37 kcal/mL of energy (20% proteins, 29% lipids [15% medium-chain triglycerides], and 51% carbohydrates). EN and PN formulas came from four different manufacturers. The complete (100%) achievement of the energy target in those assigned to receive SPN was verified twice daily.

Continuous intravenous insulin therapy to maintain blood glucose at lower than 8·5 mmol/L was provided

according to clinical protocols, and we checked arterial blood glucose frequently (as recommended and depending on the clinical situation, but at least four times a day). Hyperglycaemia was defined as a blood glucose concentration higher than 10 mmol/L, and hypoglycaemia as lower than 4 mmol/L. Trace elements, minerals, and vitamins were administered to both treatment groups daily as recommended by European guidelines.[1] Immune-enhancing enteral formula, intravenous glutamine, and omega-3 fatty acids were not administered during the trial period.

We recorded daily and cumulative energy balances from day 1 until day 8, and obtained data for follow-up variables from day 4 to day 28. Both groups continued to receive EN during follow-up, as needed. We included energy from nutritional products and from non-nutritional fluids (glucose for drug dilution, lipid from propofol) in the calculation of energy balances. A different patient computerised information data management system was used at each hospital (CliniSoft 6.2, General Electric, in Geneva; Metavision 5.45, iMDsoft, in Lausanne).

Trial endpoints

The primary endpoint was the occurrence of nosocomial infections after day 8 until day 28. Infections were defined according to definitions from the Centers for Disease Control and Prevention.[10] Five infection categories were defined: pneumonia (ventilator or non-ventilator-associated pneumonia, and other lower respiratory tract infections); bloodstream infection (laboratory-confirmed bloodstream infections and clinical sepsis); urogenital infection (device-associated or non-device-associated urinary tract and genital infections); abdominal infection (intra-abdominal infections); and other infection (skin, bone, and soft tissue infections; ear, nose, and throat infections; upper respiratory and intrathoracic infections).

The main secondary endpoints were the number of antibiotic days (defined as days from day 1 to day 28 during which a patient received at least one dose of antibiotics) for nosocomial infection and number of antibiotic-free days (days during which a patient did not receive antibiotics; if a patient died, antibiotic-free days were censored at death). Antibiotics were given to treat infection and as a prophylaxis.

Other secondary endpoints were duration of invasive and non-invasive mechanical ventilation, length of stay in the ICU and hospital until day 28, mortality in the ICU, general mortality, duration of renal replacement therapy, glycaemia (crude blood glucose concentration and area under the curve [AUC]), phosphataemia, concentration of C-reactive protein, liver test results, and drug administration (insulin, steroids, and antifungal agents).

Statistical analysis

We based sample size calculations on an assumed overall infection rate of 50% in the targeted patient population, on the basis of results from our previous study,[11] which showed an incidence of 57% of nosocomial infections in patients admitted to the ICU for more than 5 days. We postulated that full coverage of energy needs might decrease the infection rate by 33%. To detect such an effect with a statistical power level of 80%, 148 patients had to be included in each group. The intention-to-treat analysis included all patients randomly assigned to the intervention (SPN) group or control (EN) group; the per-protocol analysis (appendix) included only patients who fully completed the 5-day intervention in the ICU. Variable summaries are shown as frequency, proportion, mean (SD), or median (IQR) as appropriate. We used the Q–Q plot to assess whether continuous data were normally distributed. We did descriptive analyses with the χ^2 or Fisher's exact tests for categorical variables, and the Student's *t* test or Mann-Whitney-Wilcoxon test for continuous variables when appropriate. We used Cox

See Online for appendix

	SPN (n=153)	EN (n=152)
Age (year)	61 (16)	60 (16)
Weight (kg)	74·8 (12·9)	77·3 (15·3)
Body-mass index (kg/m²)	25·4 (3·9)	26·4 (4·6)
SAPS II score	49 (17)	47 (15)
APACHE II score	22 (7)	23 (7)
Hospital		
Geneva	99 (65%)	101 (66%)
Lausanne	54 (35%)	51 (34%)
Surgery	70 (46%)	69 (45%)
Sex (male)	110 (72%)	105 (69%)
Primary diagnosis		
Shock (all)	30 (20%)	29 (19%)
Neurological	23 (15%)	23 (15%)
Cardiac surgery	21 (14%)	18 (12%)
Polytrauma	19 (12%)	20 (13%)
Pneumonia	16 (10%)	8 (5%)
Cardiac arrest	11 (7%)	11 (7%)
Respiratory failure	8 (5%)	13 (9%)
Myocardial infarction	6 (4%)	9 (6%)
Acute pancreatitis	4 (3%)	2 (1%)
Liver failure	0	2 (1%)
Other	15 (10%)	17 (12%)
Infection at ICU admission	77 (50%)	65 (43%)
Energy target* (kcal/day)	1892 (365)	1836 (388)
Energy target per ideal bodyweight* (kcal/kg/day)	28 (4)	27 (5)
Protein target† (g/day)	81 (7)	80 (6)

Data are mean (SD) or number (%). No significant differences were identified between the two groups. SPN=supplemental parenteral nutrition. EN=enteral nutrition. SAPS II=Simplified Acute Physiology II. APACHE II=Acute Physiology and Chronic Health Evaluation II. *Measured by indirect calorimetry on day 3 in 198 (65%) of 305 patients. †As recommended in European Society for Clinical Nutrition and Metabolism guidelines (1·2 g per kg of ideal bodyweight per day).[1]

Table 1: **Baseline demographic and clinical characteristics**

proportional hazards ratios in univariable and adjusted multivariable models to compare between-group differences in the primary outcome. We selected variables for the adjusted multivariable analysis if their p value was 0·20 or lower in the univariable analysis and according to their clinical relevance. We included the following variables: SAPS II score, hospital (Geneva *vs* Lausanne), admission category (surgery *vs* medicine), antibiotic use, and mechanical ventilation before day 9. We generated survival analysis curves during 28-day follow-up using the Kaplan-Meier method. We checked proportional hazards assumptions with a test based on Schoenfeld residuals. We calculated Harrell's C index from the multivariable model to establish the concordance between estimated and observed values. We also analysed the between-group difference in the number of nosocomial infections with a multivariable Poisson regression model because the mean and the variance were equal[12] adjusted for covariates (appendix).

We used multivariable negative binomial regression models to analyse the number of antibiotic days for nosocomial infections, because this outcome had an overdispersion in the Poisson model.[13] The negative binomial model included SAPS II, hospital, and admission category as covariates. We also analysed time on mechanical ventilation with a multivariable negative binomial regression model adjusted for covariates and controlled for length of ICU stay. We did subgroup analyses for time on mechanical ventilation of infected and non-infected patients during follow-up. We analysed mortality using the Cox proportional hazards models. The length of stay, antibiotic days, and antibiotic free-days were tested with multivariable linear regression models adjusted for covariates. In case of suspicion of heteroscedasticity (unequal variances), we used Eicker-Huber-White standard errors.

We used Stata 12.0 software for all statistical analyses and set statistical significance to α=0·05. We used the false discovery rate controlling method (the Benjamini-Hochberg procedure) to correct for multiple comparisons.[14]

The protocol is registered with ClinicalTrials.gov, number NCT00802503.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We enrolled 305 patients between December, 2008, and December, 2010, 153 of whom were assigned to receive SPN, and 152 to EN only. All patients received their allocated nutritional protocol, although 20 in the SPN group and ten in the EN group discontinued the study, mostly because of protocol violation (figure 2).

Demographic and clinical characteristics of the trial groups were similar at randomisation (table 1). On day 4, the mean cumulative deficit of all patients was –3999 kcal (SD 1293) on the basis of predictive equations (–4064 [1322] in the SPN group *vs* –3880 [1332] in the EN group). The target was measured by indirect calorimetry in 198 (65%) of 305 patients, resulting in reduced targets in both groups: SPN –42 kcal (p=0·2545); EN –89 kcal (p=0·0155); overall –66 kcal (p=0·0110). Mean energy delivery between day 4 and day 8 was 28 kcal/kg per day (SD 5) in the SPN group and 20 kcal/kg per day (7) in the EN group (103% [18%] of energy target in the SPN group *vs* 77% [27%] in the EN group; p<0·0001; figure 3). The mean cumulative energy balance during the intervention period was 124 kcal (1589) in the SPN group versus –2317 kcal (2657) in the EN group (p<0·0001). Mean

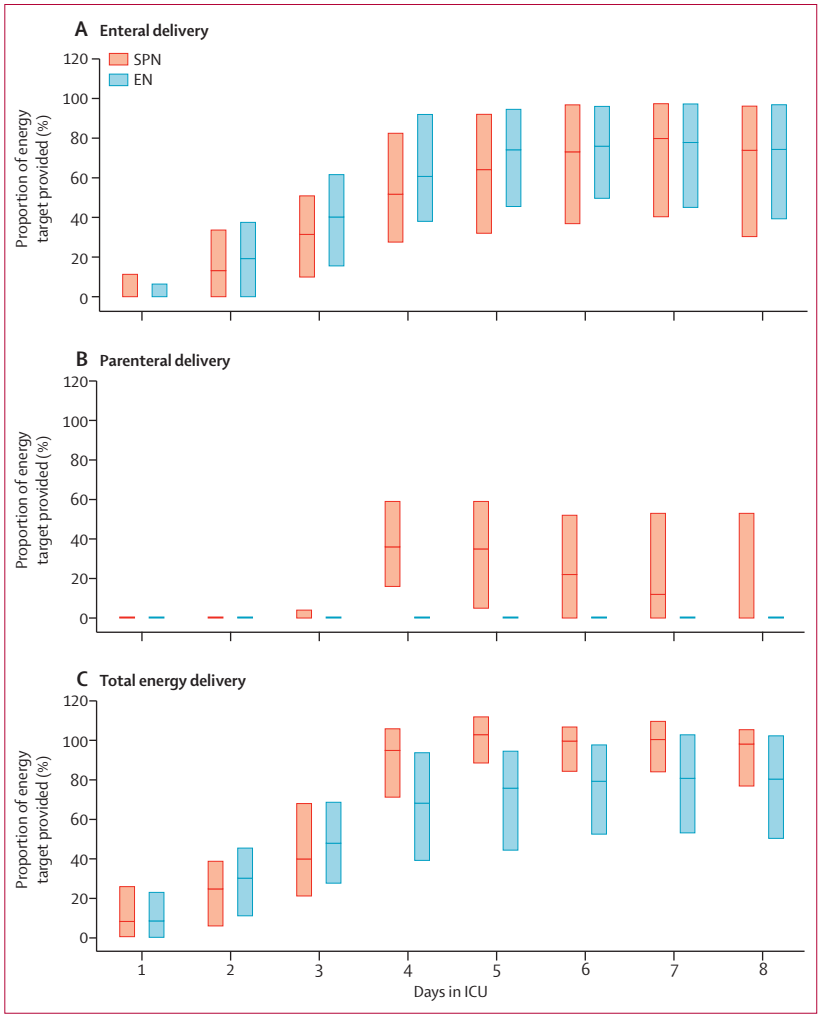

Figure 3: **Energy delivery**
Energy (nutritional products and non-nutritional fluids) expressed in percentage (%) of energy target according to method of delivery: enteral route (A), parenteral route (B), or a combination of both routes (C) in the intention-to-treat patients. Horizontal lines within the boxes show the median, and the boxes show IQR. EN=enteral nutrition. ICU=intensive-care unit. SPN=supplemental parenteral nutrition.

protein delivery between day 4 and day 8 was 1·2 g/kg per day (0·2) for the SPN group and 0·8 g/kg per day (0·3) for the EN group (100% [16%] *vs* 71% [27%]; p<0·0001).

The adjusted probability of nosocomial infection between days 9 and 28 was significantly lower in the SPN group than in the EN group (41 [27%] of 153 patients in the SPN group had a nosocomial infection during follow-up compared with 58 [38%] of 152 patients in the EN group; hazard ratio 0·65 [95% CI 0·43–0·97]; p=0·0338; table 2, figure 4). The Poisson regression model analysis also showed a significant reduction in the number of nosocomial infections in the SPN group compared with the EN group (–0·42, 95% CI –0·79 to –0·05; p=0·0248) during the 28-day follow-up (appendix).

We noted no increase in the number of bloodstream infections in the SPN group, nor a difference in the distribution of nosocomial infections, during intervention (days 4–8) and follow-up (days 9–28; table 3).

During follow-up, the mean number of antibiotics days was significantly lower in the SPN group than in the EN group, and the mean number of antibiotic-free days was higher in the SPN group (table 4).

Time on mechanical ventilation during the entire study and during follow-up only was similar in both groups, but was significantly reduced in patients without nosocomial infections (table 4). The mean lengths of stay in the ICU and hospital (table 4), frequency of hypoglycaemia and hyperglycaemia, and renal replacement therapy requirement (data not shown) did not significantly differ between groups. ICU and general mortality at day 28 was similar in both groups (table 4). During the intervention period, glycaemic AUC measurements and the amount of insulin did not differ between groups (data not shown). Throughout the study, 21911 blood glucose measurements were taken (11305 during intervention). More short episodes of hyperglycaemia occurred in patients given SPN than in patients given EN, but the AUC did not increase during the intervention period (mean blood glucose concentration 1100 mmol/L [SD 282] in the EN group *vs* 1092 mmol/L [264] in the SPN group). Daily insulin requirements did not differ between the groups, and episodes of hypophosphataemia and hyperphosphataemia were equally distributed between groups (data not shown). By day 8, aspartate aminotransferase and alanine aminotransferase plasma concentrations were similar in both groups (data not shown), but alkaline phosphatase concentrations were lower in the SPN group than in the EN group (2·01 µkat/L in SPN group *vs* 2·75 µkat/L in EN group; p=0·0131). Mean C-reactive protein concentrations did not differ significantly between groups in the intention-to-treat analysis (data not shown), but did decrease significantly more in the SPN group than in the EN group after day 8 according to the per-protocol analysis (decrease of 959·54 nmol/L in SPN group *vs* 667·44 nmol/L in EN group; p=0·0180). The use of prokinetic agents did not differ between the SPN and the EN groups (data not shown).

	Univariable analysis		Multivariable analysis*	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Sex (women *vs* men)	1·02 (0·66–1·58)	0·9265	..	..
Age (1-year increase)	0·99 (0·98–1·00)	0·1934	..	..
SAPS II score (1-point increase)	1·01 (1·00–1·03)	0·0491	..	..
Body-mass index (1-kg/m² increase)	1·04 (0·99–1·08)	0·1205	..	..
Hospital (Geneva *vs* Lausanne)	1·18 (0·78–1·78)	0·4377	..	..
Study intervention (SPN *vs* EN)	0·62 (0·42–0·93)	0·0200	0·65 (0·43–0·97)	0·0338†
Admission category (surgery *vs* medicine)	1·01 (0·68–1·50)	0·9488	..	..
Antibiotics before day 9 (yes *vs* no)	1·20 (0·70–2·05)	0·5048	..	..
Infections before day 9 (yes *vs* no)	0·84 (0·56–1·26)	0·3958	..	..
Mechanical ventilation before day 9 (yes *vs* no)	1·53 (0·94–2·50)	0·0897	..	..

Univariable and multivariable Cox regression model. SAPS II=Simplified Acute Physiology II score. SPN=supplemental parenteral nutrition. EN=enteral nutrition. *Variables in the multivariable analysis were SAPS II score, hospital, study intervention, admission category, previous antibiotic use before day 9, and mechanical ventilation before day 9. †Statistically significant with Benjamini-Hochberg correction.

Table 2: **Univariable and multivariable Cox regression model for first nosocomial infection during follow-up (primary endpoint)**

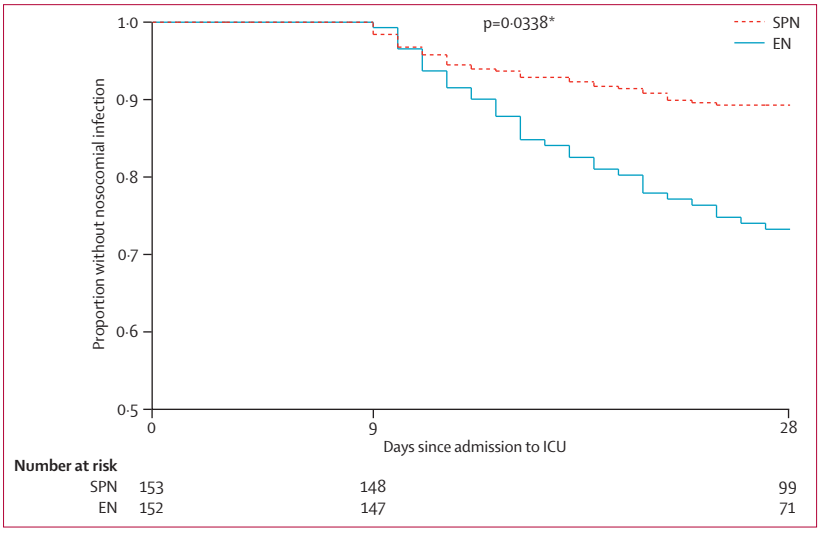

Figure 4: **Kaplan-Meier analysis of nosocomial infections**
SPN=supplemental parenteral nutrition. EN=enteral nutrition. *Statistically significant with Benjamini-Hochberg correction.

	Intervention period (days 4–8)		Follow-up (days 9–28)	
	SPN	EN	SPN	EN
Pneumonia	35 (67%)	28 (65%)	22 (46%)	32 (45%)
Bloodstream infection	10 (19%)	6 (14%)	9 (19%)	13 (18%)
Urogenital infection	4 (8%)	2 (5%)	7 (15%)	5 (7%)
Abdominal infection	1 (2%)	4 (9%)	8 (17%)	8 (11%)
Other infection*	2 (4%)	3 (7%)	2 (4%)	13 (18%)

Data are number of events (%). Patients can have one or more infections. Comparisons by type of infections were not significant for the intervention period (p=0·4866) or follow-up period (p=0·1476). SPN=supplemental parenteral nutrition. EN=enteral nutrition. *Skin, bone, soft tissue, ear, nose, throat, upper respiratory, and non-pulmonary intrathoracic infections.

Table 3: **Distribution of nosocomial infections during intervention and follow-up**

	SPN (n=153)		EN (n=152)		p value	Coefficient (95% CI)
	Mean (SD) or n (%)	95% CI	Mean (SD) or n (%)	95% CI		
Follow-up (days 9–28)						
Antibiotic days for nosocomial infections*	3 (6)	2–4	5 (7)	4–6	0·0337	−0·4 (−0·8 to −0·0)
Antibiotic days	6 (7)	4–7	8 (8)	7–10	0·0010†	−2·3 (−4·1 to −0·5)
Antibiotic-free days	14 (8)	12–15	12 (8)	10–13	0·0197	2·1 (0·3 to 3·9)
Hours on mechanical ventilation in all patients‡	60 (111)	43–81	66 (110)	49–85	0·6258	−0·1 (−0·4 to 0·3)
Hours on mechanical ventilation in patients without nosocomial infection‡	15 (59)	1–32	29 (61)	14–47	0·0028†	−1·3 (−2·1 to −0·4)
Duration of study (days 1–28)						
Antibiotic days for nosocomial infections*	5 (7)	4–6	6 (7)	5–7	0·0298	−0·3 (−0·6 to −0·0)
Antibiotic days	11 (8)	9–12	13 (9)	11–14	0·0257	−2·2 (−4·2 to −0·3)
Antibiotic-free days	15 (9)	14–17	13 (10)	11–14	0·0126	2·7 (0·6 to 4·8)
Hours on mechanical ventilation in all patients‡	153 (163)	126–178	166 (160)	138–189	0·2912	−0·1 (−0·3 to 0·1)
Hours on mechanical ventilation in patients without nosocomial infection‡	83 (101)	58–105	108 (115)	77–135	0·0747	−0·3 (−0·6 to 0·0)
Days in ICU	13 (10)	11–14	13 (11)	12–14	0·2592	−1·3 (−3·5 to 1·0)
Days in hospital	31 (23)	29–38	32 (23)	29–39	0·8781	−0·4 (−5·9 to 5·0)
ICU mortality§	8 (5%)	3–10	12 (7%)	5–13	0·2118	0·6 (0·2 to 1·6)
General mortality§	20 (13%)	9–19	28 (18%)	13–25	0·1193	0·6 (0·3 to 1·2)

Linear regression analyses were done for all secondary outcomes (adjusted for Simplified Acute Physiology II [SAPS II] score, hospital, and admission category) except for antibiotic days for nosocomial infections, hours on mechanical ventilation, and mortality. SPN=supplemental parenteral nutrition. EN=enteral nutrition. ICU=intensive-care unit. *Negative binomial regression analysis was adjusted for SAPS II score, hospital, and admission category. †Statistically significant with Benjamini-Hochberg correction. ‡Negative binomial regression analysis was adjusted for SAPS II score, hospital, and admission category, and controlled for length of ICU stay. §Cox proportional hazard ratios, adjusted for SAPS II score, hospital, and admission category.

Table 4: **Secondary outcomes during follow-up and throughout duration of study**

Discussion

Findings from this trial suggest the clinical usefulness of complementing the energy delivery of insufficient EN with a parenteral booster between day 4 and day 8 after ICU admission. The provision of close to 100% of energy requirements reduced the risk of development of nosocomial infections, the number of antibiotic days, and the duration of mechanical ventilation in patients without nosocomial infections up to day 28.

This trial is one of the first studies to show that a combined feeding strategy with exact provision of energy needs is beneficial (panel). Malnutrition and underfeeding are associated with poor outcome in patients in the ICU, especially infectious complications,[15–17] but the optimum timing of parenteral intervention is controversial because septic complications have been associated with this approach. In patients with an infection, mortality rate is higher with the use of early PN alone, or combined PN with EN, than with EN alone.[21] Furthermore, results of the Tight Calorie Control Study (TICACOS),[18] showed that EN supplemented with PN with an energy target determined by repeated indirect calorimetry measurements, adjusted from the first day of ICU admission, led to lower hospital discharge mortality than did EN supplemented with PN with targets not calculated by calorimetry, but was associated with more infections and a longer time on mechanical ventilation than was the control group.

By contrast, findings from other studies have shown that the optimisation of EN within 24–48 h of ICU admission reduces infectious complications and mortality.[2,7,19,20] In parallel to the lower infection rate in the SPN group, we also noted lower C-reactive protein concentrations in the SPN group than in the EN group, reflecting the reduced number of infectious complications. Results of our trial further reinforce the importance of energy provision by showing that delivery of near 100% of energy supply with an SPN approach can effectively decrease infections and antibiotic use.

Three factors might explain the between-group difference in the number of infectious complications in our trial: the trial protocol, in particular the initiation on day 4 of SPN; careful adjustment of energy supply, which avoided excessive energy delivery (ie, overfeeding) in the SPN group; and metabolic monitoring. Contrary to previous studies[2,9,21,22] that started PN early after admission to the ICU, we delayed PN until 4 days after ICU admission, allowing EN to progress sufficiently so as to limit the amount of PN needed. Moreover, by allowing advancement of EN delivery during the first 3 days, no attempt was made to force EN, preventing potential tracheal aspiration.[6] PN was adjusted twice daily to account for EN delivery changes. In the TICACOS trial,[18] the infections count started 48 h after ICU admission—ie, before a nutritional intervention could have achieved an effect—whereas we considered new infections only

after day 8, postulating that a minimum energy difference would be needed to achieve a clinical effect, while avoiding overfeeding.

Other infectious risk factors were strictly controlled in our study. Both ICUs apply a glycaemic control protocol,[23,24] which aims to lower metabolic and infectious complications associated with PN.[7,25] Additionally, both ICUs have protocols and checklists for central venous line insertion. In our trial, the catheter infection rate was low and similar in both groups. Indeed, the central catheter infection rate was lower than has been reported elsewhere.[26] Finally, while achieving better energy provision, we simultaneously provided higher intakes of proteins, vitamins, and micronutrients, which might also have contributed to the reduction in infection. The relation between optimum protein–energy intake and weaning time is still not well described. Compared with TICACOS,[18] we noted a shorter mechanical ventilation time for the patients given SPN. Also noteworthy is that patients in the indirect calorimetry group in TICACOS[18] were slightly overfed, because the investigators did not include non-nutritional energy delivery in their daily targets, resulting in a nearly systematic passing of the target (non-nutritional calories account for 100–400 kcal per day in our experience). We postulate that adequate energy and protein provision in the SPN group might have contributed to faster weaning from mechanical ventilation by decreasing nosocomial infections or decreasing skeletal muscle catabolism, particularly in the diaphragm, maintaining inspiratory muscle strength, and preventing weaning failures.[27]

Neither overfeeding, which causes excess carbon dioxide production, nor serious adverse events attributable to hyperglycaemia, occurred in the SPN group. These results might explain why patients in the SPN group spent less time on mechanical ventilation than did those in the EN group.[28] Indirect calorimetry optimises adequate prescription of energy, at least in the sickest patients. Phosphate deficiency has also been associated with respiratory muscle weakness and weaning failure; however, weaning failure was not an issue in our trial because phosphataemia was measured daily and treated according to the needs of individual patients.

Our results contrast with those of the Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial by Casaer and colleagues,[29] which compared prolonged semistarvation to early glucose load followed by early PN; however, the studies have several differences. Our trial assessed severely critically ill patients with indications for artificial nutrition, whereas EPaNIC studied mostly patients who had had cardiac surgery, who rarely need such support, especially PN. We looked at patients staying in the ICU for at least 5 days, whereas 50% of the patients in EPaNIC stayed in the ICU for less than 3 days (only 40·5% of patients were still in the ICU by day 5, and 29·8% by day 7, compared with 90% by day 9 in our trial). Patients in the PN group of EPaNIC were given a high early glucose load from day 1, according to local practice, whereas we started the intervention on day 4 to maximise the potential for EN delivery, in keeping with European Society for Clinical Nutrition and Metabolism guidelines.[1] Moreover, our EN group was a true control group, showing cumulative increasing energy deficit (figure 3). Our population was composed exclusively of patients with a real indication for nutritional support, with a

Panel: Research in context

Systematic review

We searched online bibliographic databases (PubMed), personal files, and relevant reference lists with the search terms "parenteral nutrition", "enteral nutrition", "critically ill" and "clinical outcome", restricting our search to articles published in English between January, 1990, and July, 2012. The meta-analysis by Simpson and colleagues[7] was the first to show that parenteral nutrition (PN) improves overall clinical outcome in patients in the intensive-care unit (ICU), although PN did increase the infection rate. Villet and colleagues[15] and Dvir and colleagues[16] showed that nutritional deficits resulting from insufficient enteral nutrition (EN) were closely associated with an increased number of complications, mostly infections, in these patients. Our group previously presented a nutritional algorithm for this critically ill population,[8] with the objective of providing 100% of the energy target from day 4 after ICU admission by supplementing EN with PN.

Two other studies explored the same hypothesis with conflicting results. The Tight Calorie Control Study (TICACOS),[18] a prospective randomised controlled study, assessed the effects of precisely calculated daily energy needs in mechanically ventilated patients in the ICU. Patients were randomly assigned either to target energy delivery, calculated by indirect calorimetry, adding PN to EN when necessary, or to routine nutritional support (25 kcal/kg per day). A non-significant decrease in post-ICU mortality was reported in patients fed according to indirect calorimetry, despite more infections and a longer duration on mechanical ventilation; of note, non-nutritional energy delivery was not incorporated into the prescription, causing overfeeding. The large, prospective, Impact of Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPaNIC) trial,[29] randomised patients to early (day 2 with glucose from day 0) versus late (day 8) PN after ICU admission, and concluded that early PN was harmful (more complications, including infections), although tight glycaemic protocol was provided for all patients.

Interpretation

Our study is the first randomised controlled trial to show that optimisation of the energy target by supplemental PN (SPN) in critically ill patients for whom EN is insufficient is associated with reduced nosocomial infections, antibiotic use, and shorter duration of mechanical ventilation. The initiation of PN on day 4 after admission, the careful adjustment of the energy supply to avoid excessive energy delivery, and close metabolic monitoring contributed to the favourable outcome and allowed good glycaemic control. The difference in outcomes between our SPN study and both TICACOS and EPaNIC could be attributed to a slight but systematic overfeeding in both trials' intervention groups, and to the inclusion in the EPaNIC trial of patients without a firm indication for nutritional therapy or PN (ie, very short ICU stay not allowing EN intolerance detection, 61% elective heart surgery, 58% stayed ≤5 days). Furthermore, an early hypertonic glucose load during the acute phase in the early PN group, and overfeeding due to the absence of indirect calorimetry, contributed to the increased rate of infections in EPaNIC.

Our findings provide evidence that individually optimised energy supplementation with SPN starting 4 days after admission should be considered as a strategy to improve clinical outcome in patients in the ICU with insufficient EN.

mean cumulative energy deficit of nearly –4000 kcal at day 4. These patients were generally more fragile, with a true risk of malnutrition, than were the patients assessed in EPaNIC.

In our trial, mortality at day 28 did not differ between groups, but the study was not powered to detect a mortality difference. Moreover, observed mortality was lower than expected mortality as predicted by the severity scores. Our data are in agreement with that from studies showing that optimised nutrition, whatever the route, decreases mortality in critically ill patients compared with insufficient nutrition provision.[7,30]

Both participating centres included a well balanced population of medical and surgical patients, and have high standards of nutritional care, shown by low cumulative energy deficits in the EN group. Almost two-thirds of patients had indirect calorimetry at day 3 after ICU admission, allowing energy delivery as close as possible to the predefined 100% energy target, preventing overfeeding. The energy target was precisely reached in the SPN group, as shown by a neutral cumulative energy balance during the intervention period. Delivery of any energy, including non-nutritional glucose and fat, was recorded by computerised systems, reducing inaccuracies in the data.

We also showed that SPN neither compromised glycaemic control nor increased insulin needs compared with EN, thereby confirming that patients in the SPN group were not overfed. Also of note is that all results were confirmed by the per-protocol analysis (appendix).

Our trial was limited by the fact that it was not double blinded by design. However, the risk of bias was reduced because the investigators worked independently from the physicians in charge of the patients. Moreover, the difference in the energy delivery between groups was small because EN patients were not underfed intentionally (pure EN during the first week reached more than 75% of energy target by day 8).[4] This percentage is higher than reported by others.[20] Furthermore, stratification for body-mass index showed no significant difference between the two groups[20] (data not shown).

Our findings could contribute to improvement of patient care by emphasising the importance of nutritional support and dedicated nutritionists. In addition to the nutritional quality improvement recorded, SPN could reduce overall health-care costs by reducing nosocomial infections, antibiotic usage, and time on mechanical ventilation, which could easily offset the costs of SPN.

Contributors

CP designed the study. CPH, MMB, SG, PD, and RT recruited patients, and CPH, MMB, and CP obtained ethical committee approval. CPH, MMB, SG, PD, RT, and CP participated in the search of the scientific literature, obtained the data, and reviewed and approved the final version of the report. WZ also helped to obtain the data. CPH, MMB, SG, WZ, RT, and CP interpreted and analysed the data, with MCC providing supervisory statistical advice. All authors helped to draft the report or critically revise the draft, and had final approval of the report.

Conflicts of interest

MMB has received research grants and consulting fees from Laboratoire Aguettant, Baxter, B Braun, Fresenius Kabi, Nestlé Medical Nutrition, and Novartis. PD was supported by an unrestricted academic research fellowship from Novo Nordisk France. RT has received consultancy fees from Baxter, B Braun, Nestlé Medical Nutrition, and Nutricia. CP has received research grants and consulting fees from Abbott, Baxter, B Braun, Cosmed, Fresenius Kabi, Nestlé Medical Nutrition, Novartis, Nutricia-Numico, Pfizer, and Solvay. CPH, SG, WZ, and MCC declare that they have no conflicts of interest.

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