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# Parenteral with enteral nutrition in the critically ill

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**Abstract** *Objective*: To determine whether nutrient intake by early enteral nutrition with parenteral nutrition improves levels of retinol-binding protein and prealbumin (primary endpoint) and reduce morbidity and mortality (secondary endpoint) in ICU patients. *Design:* Prospective, double-blind, and randomized, placebo-controlled study. *Setting:* Two intensive care units in a tertiary institution. *Patients and participants:* 120 patients in two groups of 60. *Interventions:* Patients received either enteral plus parenteral nutrition (treatment group) or enteral nutrition plus placebo (placebo group) for 4–7 days after initiation of nutritional support. *Measurements and results:* Retinol-binding protein ($P = 0.0496$) and prealbumin ($P = 0.0369$) increased significantly in the treatment group from day 0 to day 7. There was no reduction in morbidity in ICU. There was no difference in OMEGA score (263 vs. 244) and length of stay in the ICU (16.9 vs. 17.3), but a reduction in length of stay at hospital (31.2 ± 18.5 vs. 33.7 ± 27.7, $P = 0.0022$). Mortality on day 90 (17 vs. 18) and after 2 years (24 vs. 24) was identical. *Conclusions:* Although it enhances nutrient intake and corrects nutritional parameters such as RBP and prealbumin more rapidly, within 1 week, supplemental parenteral nutrition has no clinically relevant effect on outcome in ICU patients at the early phase of nutritional support.

**Key words** Parenteral nutrition · Enteral nutrition · Nutritional assessment · Clinical trial · Randomized controlled trial · Intensive care

## Introduction

Critically ill patients are hypermetabolic and require increased nutrients [1]. They develop intestinal dysfunction [2], which includes reduced intestinal motility and absorption [3], enhanced intestinal permeability, local immune impairment, bacterial translocation, and consequent multiple organ failure [4]. There is a growing body of evidence suggesting that nutritional support is clinically beneficial in these patients [5, 6]. When the oral route is impossible or insufficient, enteral support provides the nutrients necessary to maintain the gastrointestinal barrier [7]; this has a lower rate of complication [8] and is less expensive than parenteral nutrition [9]. However, it does not prevent the occurrence of multiple-organ failure after sepsis [10], and it is not known whether it improves outcome in the critically ill. In some instances, enteral nutrition falls short of providing immediate adequate amounts of required substrates, due to frequent bowel impairment [11]. The way in which this is relevant to patient outcome remains a matter of discussion.

To address this issue we conducted a two-center, prospective, double-blind, randomized, placebo-controlled study to assess the effect of an adjuvant parenteral solution [12] to early enteral nutrition on nutritional param-

**Table 1** Discharge diagnoses in both groups (treatment: enteral + parenteral, placebo: enteral + placebo parenteral)

| | Treatment $n = 60$ | Placebo $n = 60$ |
|---|---|---|
| Multiple Trauma | 25 | 22 |
| Respiratory Failure | 12 | 10 |
| Stroke | 7 | 8 |
| Sepsis | 5 | 8 |
| Coronary Artery Disease | 6 | 4 |
| Poisoning | 2 | 4 |
| Renal Failure | 2 | 2 |
| GI Bleeding | 1 | 2 |

eters, morbidity, and mortality in the critically ill. Our goal was to determine whether, during the first week of early enteral support, adjuvant parenteral supplementation [13] safely and more rapidly corrects nutritional parameters such as retinol-binding protein (RBP) and prealbumin (primary endpoint). We also determined whether this prevents or limits the occurrence of multiple organ failure, reduces the need for ventilator, circulatory, neurological, or renal support, shortens the length of stay, and reduces mortality compared with exclusive enteral support in ICU (secondary endpoints).

## Materials and methods

### Patients

Two groups of 60 patients each were enrolled between August 1996 and May 1997 and were followed up for 2 years. Those in the treatment group received both enteral nutrition and parenteral nutrition; those in the placebo group received enteral nutrition and placebo. Eligible for inclusion were all patients 18 years old or over, admitted to ICU for more than 2 days, and expected to stay alive for more than 2 days. In addition, they were expected to eat less than 20 kcal/kg daily for more than 2 days, and enteral feeding to be progressively administered for more than 2 days. Excluded was any patient admitted after elective surgery, or presenting a contraindication to enteral and/or parenteral support, or having a previous history of allergy to vitamins. There was no difference between the two groups regarding gender, age, diagnosis (Table 1), or severity of illness (Table 2). The study was performed in two intensive care units [medical (16 beds) and surgical intensive care (11 beds)] at the same university teaching hospital (900 beds).

### Nutritional support

#### *Enteral support*

Patients were bolus-fed (every 4 h, five times per day) with a standard [14], noncommercial, modular polymeric diet. The composition of the solution was protein (20%), polyunsaturated fats (30%), carbohydrates (50%), nonsoluble fibers, sodium chloride (2 g/l), potassium chloride (3 g/l), and a standard solution of hydro- and liposoluble vitamins; the concentration of the solution was 1 kcal/ml. A typical 70-kg patient would receive 100 ml initially,

**Table 2** Demographic parameters in both groups (treatment: enteral + parenteral, placebo: enteral + placebo parenteral); values are expressed as total count or mean ± SD accordingly, ns: non significant

| Parameters | Description | Treatment | Placebo | *p* value |
|---|---|---|---|---|
| Patients: | total | 60 | 60 | ns |
| Sex ratio: | Male/Female | 40/20 | 42/18 | ns |
| Age: | years | 53 ± 18 | 55 ± 18 | ns |
| Type of Admission: | Medical | 35 | 26 | ns |
| | Surgical | 25 | 34 | ns |
| Type of history: | None | 10 | 9 | ns |
| | Medical | 41 | 45 | ns |
| | Surgical | 8 | 5 | ns |
| | Obstetrical | 1 | 1 | ns |
| Mac Cabe Score: | 0, no fatality | 34 | 36 | ns |
| | 1, fatality within 5 years | 22 | 21 | ns |
| | 2, fatality within 1 year | 4 | 3 | ns |
| Knaus Score: | A, normal activity | 28 | 31 | ns |
| | B, minor impairment | 19 | 19 | ns |
| | C, moderate impairment | 9 | 9 | ns |
| | D, major impairment | 4 | 1 | ns |
| SAPS II | | 43 ± 14 | 41 ± 13 | ns |
| Height | cm | 168 ± 12 | 169 ± 10 | ns |
| Current Weight | kg | 75 ± 16 | 75 ± 15 | ns |
| Quételet Index | weight (height)$^2$ | 26 ± 5 | 26 ± 5 | ns |
| Detsky Index: | A, no malnutrition | 36 | 35 | ns |
| | B, moderate malnutrition | 17 | 21 | ns |
| | C, severe malnutrition | 7 | 4 | ns |

with an increased amount in 50-ml steps to a maximum of 350 ml every 4 h five times per day. The rate of administration was 100–150 ml/h, with a standard rinse of 50 ml (25–100 ml) water adjusted to the daily requirement assessed by daily intake and output. Residual volume was measured before each feeding; feeding was delayed by 4 h if this was more than 300 ml, and cisapride (10 mg every 6 h Propulsid, Janssen-Cilag, Issy Les Moulineaux, France) was added [15].

*Parenteral support*

Treatment consisted of a 3-in-1 solution of carbohydrates, fat, and protein, Vitrimix KV [16] and hydrosoluble vitamins, Soluvit (10 ml/l; Pharmacia & Upjohn, St Quentin-Yvelines, France). Placebo consisted of sodium chloride 0.9% with Intralipid 20% (50 ml/l) and Soluvit (10 ml/l), stable for 24 h (Pharmacia & Upjohn, St Quentin-Yvelines, France). Treatment and placebo were administered in the same type of plastic bags (1–2 l), at a concentration of 1 kcal/ml in the treatment group. The solution was administered through a central line (960 mOSm/l) [17] that was not inserted solely for nutritional purposes. The rate of intravenous administration was increased to 120 ml/h for 18–24 h.

## Methods

The objective of the study was to achieve a nutritional target intake of 25 total kcal/kg bodyweight/day (carbohydrates, fat, protein) which represents 100 kcal of carbohydrates-fat per gram of nitrogen. Using the total amount of calories we adjusted the parenteral to the enteral needs every day such that the target rate (25 kcal/kg daily) was achieved early. Patients received placebo or treatment for 4–7 days. Afterwards nutritional support was maintained only if deemed necessary.

*Assessment*

On day 0, defined as the day on which the treatment began, the following parameters were recorded: gender, age, date of admission at hospital, date of admission in ICU, date of inclusion, type of admission, past history. Two scores of underlying chronic illness were recorded (MacCabe and Jackson [18] and Knaus et al. [19]) and the Simplified Acute Physiology Score [20], a score of severity within the first 24 h in ICU. To assess any underlying malnutrition, height, usual weight, body mass index [weight/(height)$^2$], Subjective Global Assessment (SGA) or Detsky et al. score [21], and other malnutrition indices based on albumin ± weight changes such as the Buzby et al. Nutritional Risk Index (NRI) [22], and the MacClave et al. score [23] were also used. Follow-up on days 0, 4, 7, 14, 21, and 90 was performed with the Organ System Failure (OSF) score [24], weight, electrolytes, kidney, and liver function tests. On the day of discharge we noted length of stay in ICU and length of stay in hospital. We also recorded the total number of days of ventilation support, extrarenal support, and inotropic and/or vasoactive drugs support, defined as the use of one or several of these substances during a 24-h period, anytime each day. The burden of care was assessed by the OMEGA score that includes length of stay, nursing workload, severity of condition and procedures [25]. The number of nosocomial infections, defined by isolation with routine procedures (sputum, urine, blood) of at least one microbe requiring a specific treatment was also noted. On days 0, 4, 7, 14, and 21 the following nutritional parameters were assessed: lymphocyte count, albumin, prealbumin, transferrin, RBP, C-reactive protein, serum copper, plasma zinc, selenium, vitamin E, and erythrocyte glutathione.

*Cost assessment*

The cost directly related to the preparation was evaluated, taking into account the intravenous compounds (carbohydrates, fat, protein, hydrosoluble vitamins), materials (gauze, needles, syringes), and sets of transfer (lines, bags) and expressed as equivalent euros. The overall cost was calculated by the OMEGA score, which includes certain procedures recorded once during the ICU stay, some every time, and others daily [26].

*Nutritional tolerance*

Every day from day 1, defined as the day following the start of treatment, to day 7, the tolerance was assessed by the amount of enteral and parenteral diet effectively administered. Digestive complications included nausea, vomiting, distension, diarrhea, and gastric residue above 300 ml. Mechanical complications included feeding tube displacement and obstruction. Metabolic complications included sodium chloride lower than 135 or higher than 145 mEq, potassium chloride lower than 3.5 or higher than 5 mEq/l, aspartate aminotransferase higher than 35 UI/l, and total bilirubin higher than 10 mg/l. Glucose level was checked every 4 h and maintained around 1.6–2 g/l with insulin using a sliding scale.

*Early dropout*

Early dropout was defined as a patient who effectively received more than 20 kcal/kg per day before day 4, who required total parenteral nutrition, or who died between day 0 and day 4. However, these patients were not excluded from the analysis (see below).

*Statistical analysis*

The study was a prospective, double-blind, randomized, parallel, placebo-controlled study with a minimum of 4 days and a maximum of 7 days of treatment and a follow-up at day 14, 21, and 90 and 2 years. It was an intention-to-treat study, using analysis of variance for paired data and $t$ test or $\chi^2$ as appropriate on SAS software (SAS Institute, Cary, NC). The primary endpoints were the rate of correction of RBP and prealbumin after 4 and/or 7 days. One secondary endpoint was the reduction in morbidity in ICU (organ failures, care supports, nosocomial infections, and length of stay). Another secondary endpoint was the reduction in mortality on days 7, 14, 21, and 90 [27, 28], with a follow-up at 2 years (Kaplan-Meyer and log-rank test). A third endpoint was cost: related cost of the parenteral solution and calculation of the overall cost (OMEGA). Considering an $\alpha$ risk of 5% and a $\beta$ risk of 10%, assuming a hypothetical rate of correction of RBP and prealbumin of 20% with the placebo, and 50% with the treatment (one-tailed test), a minimum number of 41 patients would be required in each group. Thus 120 patients were randomly assigned to placebo or treatment groups, in blocks of 10 (5 placebo and 5 treatments). The randomization (sealed envelopes) was carried out at the central pharmacy where the bags were prepared under the label A or B. Neither the health care providers nor the patients were aware of their content. Both types of bags were opalescent by the adjunction of small amount of fat and vitamins. The statistician was also

not informed of the nature of the groups until all events had been determined (3 months after the last enrollment) and the analyses completed. Values are expressed as mean ± SD. A statistical significance was set at $P < 0.05$.

*Ethical issues*

This study was conducted according to the principles established in the Helsinki Declaration and approved by the Consulting Committee for the Protection of Patients Rights in Biomedical Research, Nancy, France (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale). Informed consent was obtained directly from the patients whenever possible, or from their relatives prior to the study.

## Results

Overall, 59% of patients were well nourished, 32% moderately malnourished, and 9% severely malnourished, with no difference between the groups as judged by SGA score. On the MacClave et al. score, 54 patients in the treatment group and 45 patients in the placebo group were hypoalbuminemic ($P = 0.031$, $\chi^2$). The NRI also showed a significant difference, with a low mean value of 78 ± 8 ($n = 38$) vs. 74 ± 12 ($n = 33$; $P = 0.043$, analysis of variance), but this score was not available for all patients.

The two groups received the same mean amount of enteral intake: 11 ± 3.3 vs. 9.9 ± 3.9 kcal/kg per day ($P = 0.25$, on day 4) and 14.8 ± 4.6 vs. 13.2 ± 4.3 kcal/kg per day ($P = 0.6$, on day 7) in treatment and placebo groups, respectively. They also received the same mean amount of theoretical parenteral intake, with an incremental increase in enteral intake and decrease in parenteral intake from day 1 to day 7. However, the true parenteral intake was obviously higher in the treatment group: 13.9 ± 2.5 vs. 1.4 ± 0.3 kcal/kg ($P < 0.0001$, on day 4) and 9.9 ± 3.1 vs. 1.1 ± 0.3 kcal/kg per day ($P < 0.0001$, on day 7). The small amount of calories in the placebo group reflected the small amount of fat. Thus the true total intake was significantly different between the treatment and the placebo group (24.6 ± 4.9 vs. 14.2 ± 6.5 kcal/kg per day, $P < 0.0001$; Fig. 1). Accordingly, the cost of parenteral nutrition for 7 days was higher in the treatment group (in euro 204 ± 119 vs. 106 ± 47, $P < 0.0001$, $t$ test). There were significantly more episodes of diarrhea during the first week in the treatment group than in the placebo group (48 vs. 27, $P = 0.02$).

The nutritional parameters with a short half-life (RBP and prealbumin) corrected more rapidly in the treated group from day 0 to day 7 ($P = 0.0496$ and $P = 0.0369$, respectively) whereas zinc and selenium corrected more slowly in both groups (Table 3). Vitamin E increased more rapidly from day 0 to day 7 in the treatment group ($P = 0.031$). Glucose control was closer in the treatment group from day 0 to day 7 ($P = 0.0392$). No major changes were observed in liver and kidney function tests.

On follow- up (Table 4) there was no change in the number of days of ventilator support, cumulative number of nosocomial infections, length of stay in ICU, OSF score, OMEGA score, or mortality after 2 years (Fig. 2). However, we did observe a reduction in the number of days of inotropic/vasoactive support; howev-

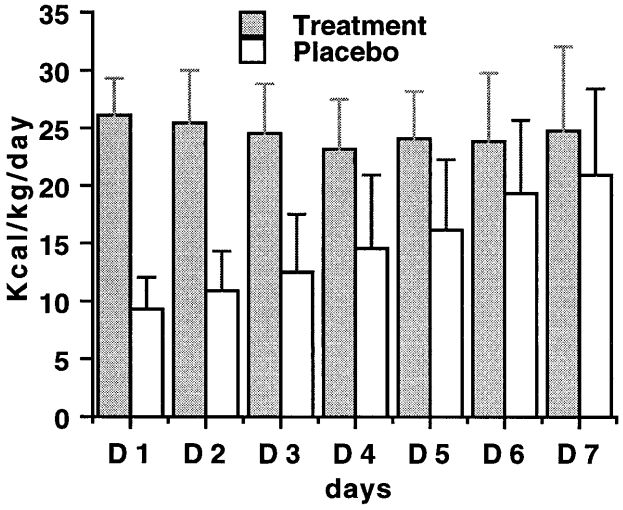


**Fig. 1** Effective caloric intake delivered in treatment group (enteral nutrition + parenteral nutrition) and placebo group (enteral nutrition + placebo). $P < 0.0001$ (analysis of variance)

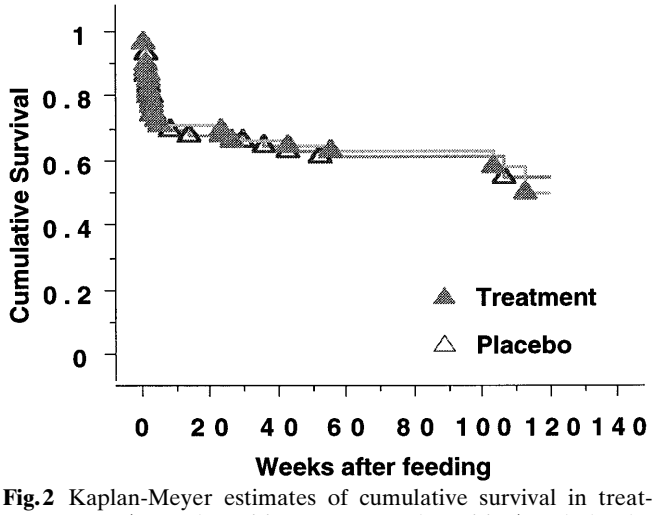


**Fig. 2** Kaplan-Meyer estimates of cumulative survival in treatment group (enteral nutrition + parenteral nutrition) and placebo group (enteral nutrition + placebo). The estimated mean survival was 61.9 ± 5.7 weeks in the treatment group (24/60 patients died) and 58.5 ± 5.6 weeks in the placebo group (24/patients died). Differences between groups were not significant ($P = 0.94$ by the log-rank test)

**Table 3** Nutritional status in both groups (T: treatment, P: placebo, numerals represent patients still under study); nv: normal values; ANOVA * $p < 0.05$ vs control; values are expressed as mean ± SD

| Parameters | Units | Group | Day 0 | Day 4 | Day 7 | Day 14 | Day 21 |
|---|---|---|---|---|---|---|---|
| T/P | | | 60/60 | 57/56 | 52/50 | 37/43 | 29/29 |
| Albumin | g/l | T | 22.4 ± 6.1 | 20.7 ± 5.6 | 22.2 ± 5.7 | 23.6 ± 5.5 | 26.8 ± 6.3 |
| (nv: 37.8–46.2) | | P | 21.7 ± 7.2 | 20.4 ± 5.9 | 21.2 ± 7.5 | 24.1 ± 6.8 | 25.2 ± 7.3 |
| Prealbumin | g/l | T | 0.11 ± 0.05 | 0.12 ± 0.06 | 0.15 ± 0.06* | 0.18 ± 0.10 | 0.20 ± 0.06 |
| (nv: 0.21–0.28) | | P | 0.12 ± 0.05 | 0.11 ± 0.05 | 0.14 ± 0.06 | 0.19 ± 0.10 | 0.19 ± 0.07 |
| Transferrin | g/l | T | 1.24 ± 0.46 | 1.32 ± 0.41 | 1.49 ± 0.44 | 1.65 ± 0.40 | 1.77 ± 0.44 |
| (nv: 1.84–2.94) | | P | 1.30 ± 0.54 | 1.29 ± 0.46 | 1.40 ± 0.44 | 1.82 ± 0.76 | 1.80 ± 0.52 |
| R.B.P. | mg/l | T | 24.8 ± 20.9 | 33.8 ± 30.5 | 40.9 ± 29.3* | 47.4 ± 21.5 | 51.8 ± 22.7 |
| (nv: 30–60) | | P | 27.1 ± 22.1 | 29.6 ± 22.2 | 36.5 ± 23.5 | 50.2 ± 21.4 | 51.9 ± 25.0 |
| C Reactive Protein | mg/l | T | 161.3 ± 99.3 | 113.8 ± 78.7 | 106.8 ± 99.5 | 68.6 ± 65.9 | 53.9 ± 54.1 |
| (nv: < 5) | | P | 161.0 ± 81.8 | 120.3 ± 81.7 | 96.8 ± 65.6 | 67.0 ± 61.2 | 65.4 ± 53.9 |
| Plasma Zinc | mg/l | T | 0.44 ± 0.19 | 0.55 ± 0.21 | 0.64 ± 0.19 | 0.79 ± 0.22 | 0.90 ± 0.23 |
| (nv: 0.70–1.10) | | P | 0.46 ± 0.23 | 0.56 ± 0.14 | 0.64 ± 0.15 | 0.84 ± 0.23 | 0.89 ± 0.19 |
| Plasma Selenium | µg/l | T | 47.0 ± 15.5 | 46.9 ± 18.0 | 50.3 ± 15.9 | 56.2 ± 17.0 | 58.1 ± 20.6 |
| (nv: 60–90) | | P | 48.0 ± 15.7 | 49.8 ± 15.6 | 51.4 ± 15.2 | 61.0 ± 18.3 | 57.8 ± 17.7 |
| Vitamin E, total | mg/l | T | 9.9 ± 4.5 | 13.3 ± 3.8 | 12.3 ± 3.6* | 12.5 ± 4.0 | 13.0 ± 3.5 |
| (nv: 8.0–19.0) | | P | 9.8 ± 4.6 | 11.7 ± 3.6 | 11.4 ± 3.6 | 12.6 ± 3.5 | 14.1 ± 3.7 |
| Vitamin E, free | mg/l | T | 8.6 ± 3.7 | 12.2 ± 3.5 | 10.9 ± 3.2* | 11.1 ± 3.6 | 11.5 ± 3.1 |
| (nv: 8.0–17.0) | | P | 8.5 ± 3.7 | 10.1 ± 3.3 | 10.0 ± 3.1 | 11.3 ± 3.6 | 12.5 ± 3.4 |
| Glycemia | g/l | T | 1.34 ± 0.56 | 1.29 ± 0.39 | 1.16 ± 0.36* | 1.16 ± 0.48 | 1.02 ± 0.24 |
| (nv: 0.75–1.15) | | P | 1.60 ± 0.71 | 1.31 ± 0.49 | 1.31 ± 0.62 | 1.25 ± 0.59 | 1.13 ± 0.36 |

er, a single patient in the placebo group accounted for the difference (49 days), and when this patient was excluded, the difference disappeared (3.78 ± 18.8 vs. 3.7 ± 18.5 days, $P = 0.95$). The length of hospital stay was also shorter (Fig. 3).

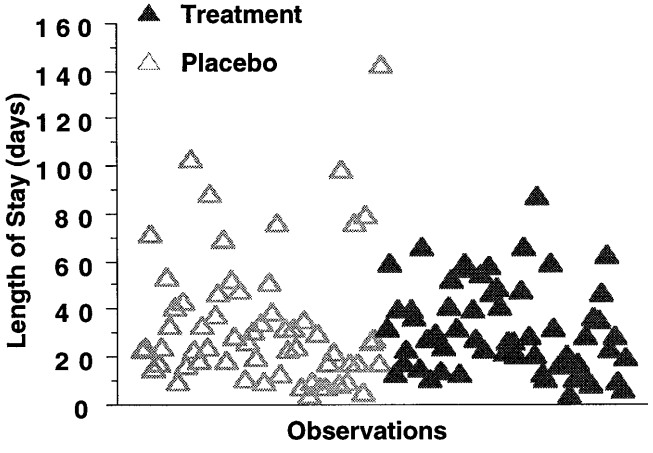


**Fig. 3** Univariate scattergram for the length of stay at hospital in treatment group (enteral nutrition + parenteral nutrition) and placebo group (enteral nutrition + placebo). $P = 0.0022$, analysis of variance

## Discussion

The indication for nutritional support in ICU patients is still based on clinical judgment. Although no study has unequivocally demonstrated the benefit of nutritional feeding versus fasting during the first 7–10 days in ICU, severe malnutrition is now recognized as a major concern in the critically ill [29]. Early enteral feeding has been shown to improve intestinal and general immunity in these patients, is more cost-effective, and has less deleterious effects than parenteral nutrition [30, 31]. The disadvantage of enteral support is that it carries the risk of inadequate energy intake. A recent survey [32] reported that the proportion of nutrients actually delivered was only 75% with enteral nutrition and 88% with parenteral nutrition. The main problem in achieving tolerance with enteral support seems to be related to gut dysfunction, elective stoppage of procedures, and the lack of a defined feeding protocol [33]. Current recommendations advocate starting enteral nutrition early [34].

The overall time between admission to the ICU and nutritional support was 1.3 ± 1.6 days. All 120 patients received an average of 13.7 ± 7.3 kcal/kg enterally per day, representing 714 days of nutritional support, with 102 (85%) patients still on nutritional support on day 7. During the first week of feeding the treatment group received a daily average of 24.6 ± 4.9 kcal/kg of total energy for 356 cumulative days of treatment whereas

**Table 4** Outcome in both groups (treatment and placebo); values are expressed as total count or mean ± SD accordingly; one-way analysis of variance; ns, non significant

| Parameters | Treatment | Placebo | *p* value |
|---|---|---|---|
| Patients | 60 | 60 | ns |
| Time Before Admission in ICU (days) | 3.1 ± 5.7 | 2.9 ± 6.9 | ns |
| Time Before Inclusion (days) | 1.1 ± 1.2 | 1.5 ± 1.9 | 0.0002 |
| Early Dropout | 6 | 7 | ns |
| per os before D4 | 3 | 3 | ns |
| death before D4 | 3 | 4 | ns |
| Adverse Events | 5 | 3 | ns |
| Length of Stay in ICU (days) | 16.9 ± 11.8 | 17.3 ± 12.8 | ns |
| Length of Stay at Hospital (days) | 31.2 ± 18.5 | 33.7 ± 27.7 | 0.0022 |
| Ventilatory Support (days) | 11 ± 9 | 10 ± 8 | ns |
| Inotropic/Vasoactive Support (days) | 3.8 ± 4.3 | 4.4 ± 7.2 | 0.0001 |
| Dialysis (days) | 0.8 ± 2.4 | 0.9 ± 2.3 | ns |
| Nosocomial Respiratory Infections | 28 | 23 | ns |
| Nosocomial Urinary Tract Infections | 11 | 16 | ns |
| OSF Score on Day 0 | 1.8 ± 0.8 | 1.7 ± 0.9 | ns |
| OSF Score on Day 4 | 1.4 ± 1.1 | 1.2 ± 0.9 | ns |
| OSF Score on Day 7 | 0.9 ± 0.9 | 1.0 ± 0.9 | ns |
| OSF Score on Day 14 | 0.9 ± 1.0 | 0.7 ± 0.9 | ns |
| OSF Score on Day 21 | 0.4 ± 0.6 | 0.6 ± 0.8 | ns |
| Mortality on Day 90 | 17 | 18 | ns |
| OMEGA Score | 263 ± 183 | 244 ± 163 | ns |
| Direct Cost (EUR)/Patient/7 Days | 204 ± 119 | 106 ± 47 | 0.0001 |

the placebo group received only 14.2 ± 6.5 kcal/kg per day of total energy, for 358 cumulative days of treatment. Our hypothesis was that this difference of 10 kcal/kg per day for 7 days would show a difference in RBP and prealbumin (primary endpoint), and that this would be related to outcome (secondary endpoint) in a heterogeneous population of surgical and medical ICU patients.

Nutritional assessment in the critically ill is still a controversial issue [35]. Some indicators, such as anthropometrics, lack accuracy, and others, such as plasma concentrations of hepatic protein, lack specificity and are affected by the patient's underlying condition and/therapeutic interventions. After 7 days of feeding, RBP and, to a lesser degree, prealbumin were significantly improved in the treatment group. The most significant improvement occurred after 3 days of treatment, on day 4. This corresponded to the period when the highest level of energy was given: 26, 25, and 24 kcal/kg per day on days 1, 2, and 3, respectively in treatment, versus 9, 11, and 12 kcal/kg per day in the placebo group, the main difference being related to parenteral supplementation. Energy balance, but not fluid balance may have affected changes in RBP and prealbumin, since patient weights did not change during the first week [36]. The differences in these serum proteins, however, were small and of limited duration. Other biological changes, such as glucose and plasma vitamin E levels, seemed directly correlated with the parenteral solution.

There were no major changes in primary outcome (i.e., short-term or long-term mortality and length of stay in ICU). Only the length of stay at hospital was different in the treatment group. However, a shorter period before inclusion in this study may have been important in this group. Length of stay may also vary with other factors and is usually a weak indicator of outcome. Diarrhea was also more frequent in the treatment group, for no obvious reason.

It is generally accepted that early mortality is related to the extent of the disease process, and late mortality at 6 months may be influenced, at least in part, by nutritional support [37]. Three parameters seem to be of paramount importance in influencing patient outcome: (a) route of administration, (b) delay before feeding, and (c) the nature of the nutrient formula [38]. Assuming that early enteral support is the best option in ICU patients, many advantages were anticipated in a combined approach using both parenteral and enteral feeding: an immediate energy balance and diminished intravenous fat emulsion. These limit the risk of immunosuppression [39], the expenses, and the length of stays in hospital. Regarding the overall cost (roughly estimated by OMEGA scores), there was no difference between the two groups, if we exclude an excess of euro 204, the costs re-

lated to the parenteral solution in the parenteral supplemented group.

Supplemental parenteral feeding coupled with early enteral support is a safe and effective means of achieving an optimal caloric uptake earlier than enteral feeding alone. It also more rapidly corrects some nutritional parameters such as RBP and prealbumin within 1 week of treatment. This combined nutritional support may provide a protective window necessary for enteral nutrition to restore intestinal function. However, it does not seem to be of clinical importance in an otherwise well nourished patient, and there is no evidence to support its use during the first week of nutritional support. Whether such a supplementation could improve outcome in severely malnourished patients remains to be elucidated.

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