Influence of n-3 Polyunsaturated Fatty Acids Enriched Lipid Emulsions on Nosocomial Infections and Clinical Outcomes in Critically Ill Patients: ICU Lipids Study

Teodoro Grau-Carmona, MD, PhD[1]; Alfonso Bonet-Saris, MD[2]; Abelardo García-de-Lorenzo, MD, PhD[3]; Carmen Sánchez-Alvarez, MD, PhD[4]; Angel Rodríguez-Pozo, MD, PhD[5]; José Acosta-Escribano, MD[6]; Eduardo Miñambres, MD, PhD[7]; Jose Ignacio Herrero-Meseguer, MD[8]; Alfonso Mesejo, MD[9]

Objective: n-3 polyunsaturated fatty acids (contained in fish oil) have been shown to beneficially influence infection rate and clinical outcomes in surgical patients probably due to their immunomodulatory action. In contrast, study results of fish oil administration in critically ill patients are controversial. The aim of this study was to investigate the effects of n-3 polyunsaturated fatty acids on the prevalence of nosocomial infections and clinical outcomes in medical and surgical critically ill patients.

Design: Prospective, multicenter, randomized, comparative, double-blind study.

Setting: Seventeen Spanish ICUs during 4 years.

Subjects: A total of 159 medical and surgical intensive care patients with Acute Physiology and Chronic Health Evaluation II score more than or equal to 13, expected to require total parenteral nutrition for at least 5 days.

Interventions: Patients received total parenteral nutrition prepared either with a lipid emulsion containing 10% fish oil or a fish oil–free lipid emulsion. The prevalence of nosocomial infections was detected during 28 days of ICU stay. Patients were followed 6 months after discharge from the ICU for length of hospital stay, hospital mortality, and 6-month mortality.

Measurements and Main Results: The number of patients with nosocomial infections was significantly reduced in the fish oil–receiving group (21.0% vs 37.2%, $p = 0.035$) and the predicted time free of infection was prolonged (21 ± 2 vs 16 ± 2 d, $p = 0.03$). No significant differences were detected for ICU, hospital, and 6-month mortality.

Conclusions: The results show that administration of n-3 polyunsaturated fatty acids reduces the risk of nosocomial infections and increases the predicted time free of infections in critically ill medical and surgical patients. The administration of n-3 polyunsaturated fatty acids was safe and well tolerated. (*Crit Care Med* 2014; XX:00–00)

Key Words: critically ill patients; fish oil; nosocomial infections; total parenteral nutrition

[1]Intensive Care Unit, Hospital Universitario Doce de Octubre, Madrid, Spain.

[2]Intensive Care Unit, Clinica Girona, Girona, Spain.

[3]Intensive Care Unit, Hospital Universitario La Paz, Madrid, Spain.

[4]Intensive Care Unit, Hospital General Universitario Reina Sofía, Murcia, Spain.

[5]Intensive Care Unit, Hospital Universitari Arnau de Vilanova, Lleida, Spain.

[6]Intensive Care Unit, Hospital General Universitario de Alicante, Alicante, Spain

[7]Intensive Care Unit, Hospital Universitario Marqués de Valdecilla, Santander, Spain.

[8]Intensive Care Unit, Hospital Universitario de Bellvitge, Barcelona, Spain.

[9]Intensive Care Unit, Hospital Clinico Universitario, Valencia, Spain.

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For information regarding this article, E-mail: teodoro.grau@salud.madrid.org

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During the last decade it has been recognized that lipid emulsions, administered within parenteral nutrition (PN) as a source of energy and polyunsaturated fatty acids (PUFAs), exert an influence on immune functions depending on their fatty acid (FA) composition, namely the contents of n-6 PUFAs (main source being soy bean oil) and

n-3 PUFAs (derived from fish oil [FO]) (1). Both n-6 and n-3 PUFAs are essential FAs, and besides their function as a source of energy, they are components of cellular membranes and are metabolized into bioactive mediators (2).

Several mechanisms may underlie the immunomodulatory actions of PUFAs (3). PUFAs are incorporated into the cell membrane of immunologic cells and influence membrane fluidity and lipid raft organization, thereby altering structure and function of membrane-bound proteins (e.g., receptors, enzymes, and transporters), eventually affecting cell signaling (4–6). Furthermore, n-6 and n-3 PUFAs compete for the enzymatic transformation into eicosanoids, lipid inflammatory mediators. Eicosanoids derived from n-6 PUFAs (i.e., 2-series prostaglandins and thromboxanes, 4-series leukotrienes) are potent proinflammatory mediators, whereas those derived from n-3 PUFAs (i.e., 3-series prostaglandins and thromboxanes, 5-series leukotrienes) are less inflammatory (2). It has also been suggested that eicosapentanoic acid and docosapentanoic acid modulate inflammatory cytokine production via inhibition of nuclear factor-κ B activation (7–9). In addition, n-3 PUFAs have been shown to be metabolized into resolvins and protectins that play an important role in the resolution of inflammation (10). n-3 PUFA-induced immunomodulation is thought to reduce the inflammatory response without negatively affecting immune function (11, 12).

Several clinical trials have shown beneficial effects of parenteral FO supplementation in surgical patients, including modulation of inflammatory markers, reduced length of hospital stay, and reduced infectious morbidity (13–20). Although these findings suggest that critically ill patients may also benefit from potentially anti-inflammatory properties of n-3 PUFAs, data derived from this patient population remain controversial (3, 21). A recently published meta-analysis based on 23 studies extends the beneficial effects of parenteral n-3 PUFAs administration in surgical patients to ICU patients with respect to modulation of inflammatory markers and reduced length of ICU and hospital stay. However, a statistically significant reduction of the infection rate could not be endorsed for the ICU population (22).

This clinical trial was designed to assess whether n-3 PUFAs-enriched lipid emulsions administered as part of PN reduce infection rate and improve clinical outcomes in medical and surgical ICU patients. The primary endpoint of this study was the prevalence of hospital-acquired infections. Secondary endpoints were lengths of ICU/hospital stay and mechanical ventilation (MV), ICU/hospital mortality and 6-month mortality, and safety of administration and nutritional efficacy.

MATERIALS AND METHODS

Study Design

The study was designed as a prospective, multicenter, randomized, comparative, double-blind study in 17 Spanish ICUs. The protocol was approved by the clinical research ethics committees of all participating sites and by the Spanish Drug Agency in accordance with the principles of the Declaration of Helsinki, recommendations for Good Clinical Practice and current Spanish regulations. Voluntary informed written consents were obtained from all patients or their relatives. BBraun Medical S.A. (Barcelona, Spain) sponsored the study but funding sources had no role in the acquisition, analysis, or interpretation of data or in the submission of this report (Study registration: EudraCT [2005-003542-33]; ClinicalTrials.gov, NCT00396461).

Patient Population

Patients included (≥ 18 yr old, male and female, admitted to ICU with Acute Physiology and Chronic Health Evaluation [APACHE] II ≥ 13) were expected to require total PN (TPN) for at least 5 days according to the guidelines of the *American Society for Parenteral and Enteral Nutrition* (23) (**online supplement**, Supplemental Digital Content 1, http://links.lww.com/CCM/B46). A detailed listing of all exclusion criteria is provided in online supplement (Supplemental Digital Content 2, http://links.lww.com/CCM/B47).

Interventions and Nutritional Regimen

Patients were randomly assigned to receive TPN either prepared with the study lipid emulsion (Lipoplus; BBraun Medical S.A.), containing 50% medium-chain triglycerides (MCT), 40% soybean oil (long-chain triglycerides, LCT), and 10% FO (MCT/LCT/FO), or prepared with the control lipid emulsion (Lipofundina; BBraun Medical S.A.), a standard lipid emulsion containing 50% MCT and 50% LCT (MCT/LCT). Both lipid emulsions contained the same amount of phospholipids, phosphate, and glycerol. Randomization was computer-based, that is, randomization numbers were generated using an allocation program assuring balanced groups regarding prognostic factors (APACHE II score, < 20 and ≥ 20) and presence of sepsis at admission (24, 25). To assure double-blind testing, only the hospital's pharmacy service was able to deduce the kind of lipid emulsion assigned. All investigators, doctors, nurses, and sponsor were blinded to treatment assignation. Isocaloric and isoproteic TPN regimens were prepared in 3-in-1 bags by the hospital's pharmacy service. Total caloric intake for treatment and control group were 25 kcal/kg/d in nonseptic patients and 30 kcal/kg/d in patients with sepsis. Forty percent of caloric intake was covered by lipids up to a total of 1.5 g/kg body weight (BW) per day. Protein intake in both groups was 1.5 g/kg BW. Remaining caloric intake was covered by glucose, up to 3 mg/kg/min. Trace elements were administered according to the hospital protocol and vitamins were given from the first day of study enrollment. TPN was administered by a central venous catheter using a volumetric infusion pump. The duration of TPN was determined by the clinical condition and underlying disease of the patient, but according to the protocol, the diet prescribed was administered for at least 5 days. Enteral nutrition (EN) (up to 50% of caloric requirements) with standard enteral diet (with or without fiber) was allowed. Enteral diets did not contain any components known to exert an immune-modulatory effect. Further treatment of patients was performed according to the standards of practice

at each center. Investigators were encouraged to follow the Surviving Sepsis Campaign guidelines for patients with sepsis and the Acute Respiratory Distress Syndrome (ARDS) Network guidelines for patients with ARDS. Surveillance microbiological samples were taken at admission and every Monday and Thursday until discharge.

Primary Outcome

The primary endpoint was the prevalence of nosocomial infections (NIs) during 28 days of ICU stay (starting with the initiation of TPN, finalized before day 28 in the event of death or ICU discharge). Mechanical ventilation-associated pneumonia (VAP), bacteremia, endocarditis, mediastinitis, meningitis or ventriculitis, surgical wound infection, intra-abdominal abscess, and urinary infection were diagnosed according to previous definitions (26, 27) (online supplement, Supplemental Digital Content 3, http://links.lww.com/CCM/B48). Time free of infection (TFI) was calculated as timeframe between the first treatment day and the onset of the first episode of NI, death, or ICU discharge (maximal TFI, 28 d). Antibiotics-free time was also recorded.

Secondary Outcomes

Secondary endpoints were ICU mortality, length of ICU stay, days of MV, nutritional efficacy, and liver function (concluded from adverse reactions [ARs] related to liver function and required action/medication). Hepatic dysfunctions were further differentiated into cholestasis, liver necrosis, and mixed injury (28) (**Table 4-1**, Supplemental Digital Content 4, http://links.lww.com/CCM/B49). Patients were followed 6 months after ICU discharge for length of hospital stay, hospital mortality, and 6-month mortality.

Data Management and Statistics

Study data were collected online using an electronic case report form, linked to a database for storage and data quality control. Blind statistical analyses were performed by independent statistical staff (Department of Medicine, School of Medicine, University of Lleida, Spain) using PASW (PASW Statistics, SPSS, Madrid, Spain) and Microsoft Excel (Microsoft, Madrid, Spain). The analysis was done by intent-to-treat.

Sample-size calculation was based on the results of a previous study of our group showing the prevalence of NIs of 45% in an unselected group of patients requiring TPN (29). Assuming an α risk of 0.05 and a β risk of 0.20, the number of patients treated in each group was estimated to be 88. Considering a loss of 20%, the number of cases was determined to be 106 for each group. A reduction of the prevalence of NIs by 20% in the treatment group was defined as clinically relevant. An interim analysis was planned after recruitment of 60% of the required number of patients.

If not otherwise stated, quantitative data are expressed as mean $\pm$ SD, and qualitative data are given as absolute and relative frequencies. The prevalence of NIs, ICU mortality, hospital mortality, and 6-month mortality, as well as hepatic dysfunction and nutritional efficacy, were analyzed using the nonparametric Fisher exact test. Multivariate logistic regression was performed to investigate the relation between the prevalence of NIs and gender, age, prognostic variables, and nutritional regimen. Antibiotic-free days, length of MV, and ICU and hospital stay were analyzed using nonparametric Mann-Whitney test. TFI and survival time were estimated using Kaplan-Meier method and log-rank test was applied to test for statistical significance. TFI was estimated using the Kaplan-Meier method only including patients without signs of infection on the first and second day after enrolment. For ICU mortality and the inverse relationship with NIs, we performed a competitive risk analysis. All statistical tests were two-tailed and p values of less than 0.05 were considered statistically significant.

RESULTS

Study Population and Analysis of Baseline Characteristics

Among 3,610 consecutive ICU patients (including acute coronary syndromes) who required initiation of PN during the recruitment period (December 2006 to March 2011), 175 patients were eligible and underwent randomization. Sixteen patients withdrew informed consent or were withdrawn by the investigator after randomization. Thus, 159 patients were included for intent-to-treat analysis: 81 in the treatment group and 78 in the control group (**Fig. 1**). Demographic data, APACHE II score, and the presence of sepsis or cancer at admission were similar in both groups (**Table 1**). Solely the number of patients with acute pancreatitis differed significantly being nearly three times higher in the treatment group than in the control group (5 and 14 patients in control and treatment group, corresponding to 6.4% and 17.3%, respectively; $p = 0.049$).

Prevalence of NIs

The number of patients with at least one NI was significantly reduced in the treatment group compared with the control group: 17 of 81 patients (21.0%) in the treatment group and 29 of 78 patients (37.2%) in the control group ($p = 0.04$) (**Fig. 2**). The NI risk of patients receiving the MCT/LCT/FO lipid emulsion was reduced by more than 40% compared with the risk of patients receiving the standard MCT/LCT lipid emulsion (risk ratio [RR] = 1.8; 95% CI, 1.06–2.96). Multivariate logistic regression confirmed a reduced NI risk for patients in the treatment group (RR = 0.4; 95% CI, 0.19–0.86; $p = 0.019$).

We were unable to find significant differences between groups when looking at the different NIs. Solely the prevalence of VAP was reduced in mechanically ventilated patients without reaching significance. Antibiotic-free days were higher in the FO group (1.7 vs 1.2 d) without achieving significant differences (**Table 2**).

TFI

Among the patients without signs of infection on the first and second day after study enrolment, 13 of 71 patients (18.3%) in the treatment and 25 of 68 patients (36.8%) in the control group experienced episodes of NIs ($p = 0.022$; RR = 2.01; 95%

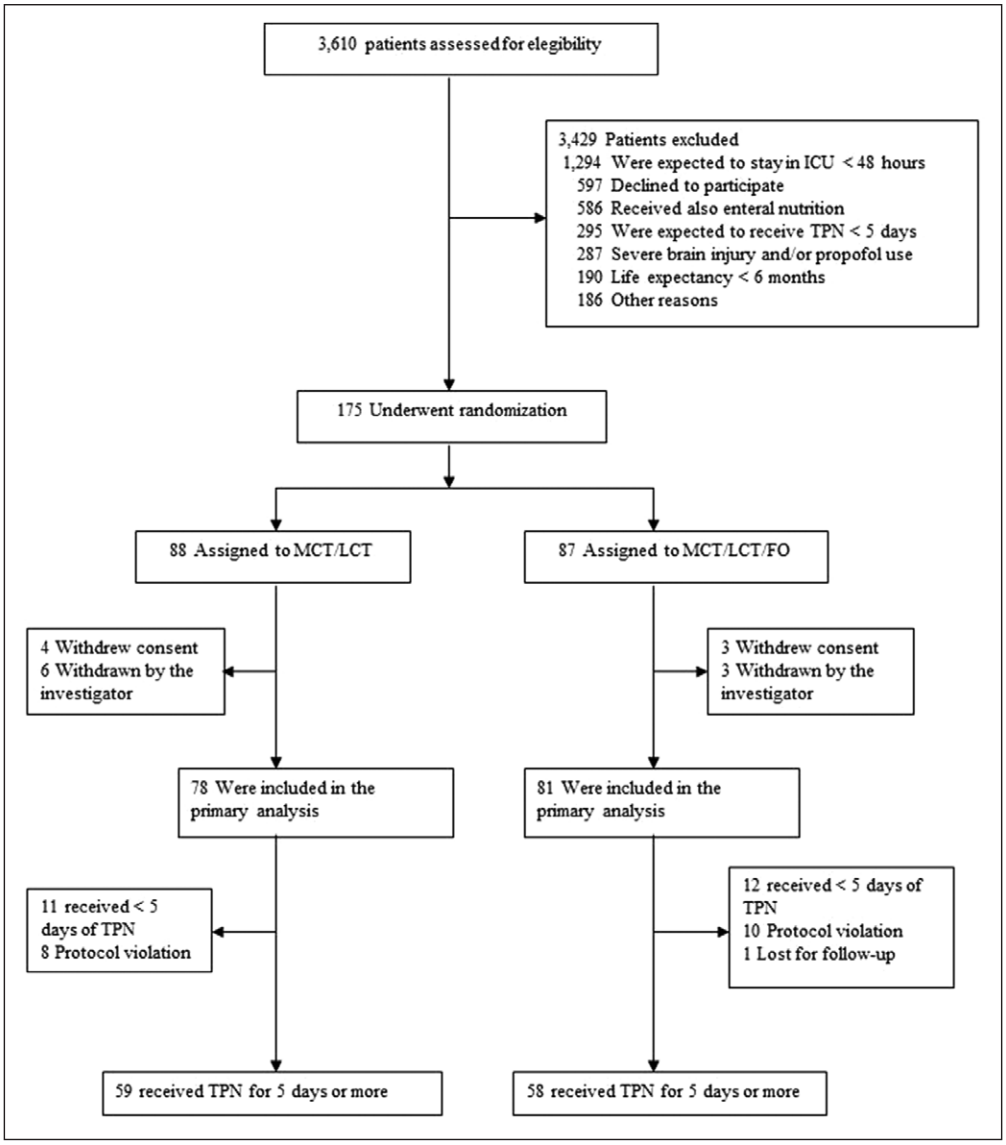

Figure 1. Patient flow according the Consolidated Standards of Reporting Trials statement. FO = fish oil, LCT = long-chain triglyceride, MCT = medium-chain triglyceride, TPN = total parenteral nutrition.

CI, 1.12–3.59). TFI in this subpopulation (estimated using the Kaplan-Meier method) was about 5 days longer in the treatment group than in the control group: 21 ± 2 days (95% CI, 17.8–25.1) and 16 ± 2 days (95% CI, 12.4–20.1) for treatment and control group, respectively. Log-rank test revealed statistical significance of this difference ($p = 0.03$) (**Fig. 3**).

Other Clinical Outcomes

Length of MV and ICU and hospital stay were shorter in the FO-receiving group, but these tendencies did not reach statistical significance. There were no statistically significant differences for ICU, hospital, and 6-month mortality (**Table 3**). Nevertheless, patients with pancreatitis receiving FO had a nonsignificant but clinically relevant mortality (20% in the MCT/LCT group vs 50% in the FO group). Patients dead from pancreatitis represented the 27% of the overall mortality in the FO group. The results of the Competing Risks Survival Analysis confirm that FO diet protects against infection regardless of the observed mortality (subdistribution hazard ratio, 0.51; 95% CI, 0.29–0.91; $p = 0.023$).

Safety of Administration and Nutritional Efficacy

No serious ARs, unexpected ARs, or serious unexpected ARs have been reported (online supplement, Supplemental Digital Content 5, http://links.lww.com/CCM/B50). The prevalence of hepatic dysfunction did not differ between groups. In each group, adverse events related to hepatic dysfunction were reported for 60 patients. TPN was continued without alteration in 95% of these patients in the treatment group and in 93% in the control group. Only 6.7% of patients with hepatic dysfunction in both groups required a specific treatment. No difference was detected regarding the prevalence of cholestasis, liver necrosis, and mixed injury between groups (**Table 4**).

There was no difference between groups with respect to nutritional intake via the parenteral route and duration of PN. During ICU stay, EN was initiated in 53% of the patients in the treatment group and 55% of the patients in the control group. The impact of TPN (energy supply exclusively via the parenteral route) and mixed nutrition (i.e., PN combined with EN) was similar between groups: nutritional requirements were covered by TPN on 78% ± 27% of the days with nutritional support in the treatment group and on 78% ± 26% of the days in the control group ($p = 0.9$) (**Table 5**).

DISCUSSION

The main finding of the current study is that administration of ~0.1 g FO/kg BW per day in combination with MCT and LCT in a lipid emulsion significantly reduced the risk of NIs (37.2% vs 21.0%) and significantly increased the predicted TFI for 5 days (16.2 vs 21.4 d) in medical and surgical ICU patients. This is in line with findings of a study performed with 38 surgical intensive care patients that showed (although not significant) a reduced infection rate after FO supplementation (41.7% vs 27.8%) (31). Reduced infection rate found in the current study

TABLE 1. Baseline Characteristics of Study Groups

Variable	MCT/LCT (Control Group), *n* = 78	MCT/LCT/Fish Oil (Treatment Group), *n* = 81	*p*
Age	60.59 ± 16.37	60.70 ± 17.29	0.844
Gender, male/female (*n*)	54/24	62/19	0.372
Weight (kg)	76.6 ± 11.1	76.9 ± 11.9	0.957
Height (m)	1.68 ± 0.09	1.70 ± 0.08	0.175
Body mass index (kg/m^2)	27.1 ± 3.9	26.6 ± 4.0	0.358
Nutritional risk index[a]	71.4 ± 14.9	69.4 ± 15.3	0.445
Acute Physiology and Chronic Health Evaluation II score	21 ± 6	21 ± 5	0.742
Sequential Organ Failure Assessment score	7.0 ± 3.3	6.8 ± 3.6	0.553
Albumin[b]	2.41 ± 0.59	2.42 ± 0.81	0.902
C-reactive protein[c]	47.65 ± 85.27	46.39 ± 89.36	0.500
Patients with cancer (%)	8 (10.3)	6 (7.4)	0.585
Patients with sepsis (%)	37 (47.4)	36 (44.4)	0.752
Patients with septic shock (%)	23 (62.2)	23 (63.9)	1.000
Type of ICU patient (%)			0.751
Medical	36 (46.2)	40 (49.4)	
Surgical	42 (53.8)	41 (50.6)	
Urgent	35 (83.3)	35 (85.4)	1.000
Patients with injuries (%)	12 (15.4)	15 (18.5)	0.675
Patients with pancreatitis (%)	5 (6.4)	14 (17.3)	0.049
Patients with infections at enrollment and/or the subsequent 2 d (%)	10 (12.8)	10 (12.3)	1.000

MCT = medium-chain triglyceride, LCT = long-chain triglycerides.
[a]Calculated as 1.519 × serum albumin in g/L + 0.417 × (current/usual weight) × 100 (30).
[b]*n* (MCT/LCT) = 65, *n* (MCT/LCT/ fish oil [FO]) = 70.
[c]*n* (MCT/LCT) = 77, *n* (MCT/LCT/FO) = 81.

could not be attributed to a specific type of NI. The risk of VAP in mechanically ventilated patients and the risk of intra-abdominal abscess in surgical patients were reduced, but these findings were not statistically significant. Sample size might be too small to allow differentiation between specific types of NIs. The potentially reduced prevalence of VAP correlates well with findings from other groups that showed improved respiratory function in critically ill patients receiving n-3 PUFA-enriched diets (32, 33). Also, there was a trend to more antibiotic-free days in the FO group. Probably, the systematic use of the selective digestive decontamination as a part of the pneumonia-zero campaign has led to misleading results because all mechanically ventilated patients received antibiotics in the first 2 days after admission.

PN, rich in n-3 PUFAs, has been shown to modulate the immune response in surgical patients via inhibition of pro-inflammatory cytokine production (13, 14) and alteration of the balance between pro- and anti-inflammatory cytokines (15–17, 31), eventually attenuating or preventing hyperinflammatory reactions. Beneficial effects of parenteral n-3 PUFAs supplementation on clinical outcomes of surgical patients including shorter length of ICU and hospital stay, as well as reduced postoperative infection rate, have been demonstrated and confirmed by meta-analyses (34, 35). Other patient groups at risk of hyperinflammatory reactions are patients with severe illness or sepsis. Several clinical trials have shown that parenteral n-3 PUFAs administration also modulates the immune response in this patient group. It was shown that FO administration increases the level of free n-3 PUFAs in patients with sepsis within 2 days, reverses the n-6/n-3 ratio, and leads to rapid incorporation of n-3 PUFAs into mononuclear leukocyte membranes (36), finally resulting in altered pro- and anti-inflammatory cytokine production (32, 33, 37, 38). Beneficial effects of n-3 PUFAs on clinical outcomes of critically ill patients were first suggested by an uncontrolled open-label study including among others patients with peritonitis and abdominal sepsis. The authors reported beneficial effects on survival, infection rate, and length of ICU and hospital stay when FO was administered in doses between 0.1 and 0.2 g/kg/d (39). So far other clinical trials failed to detect

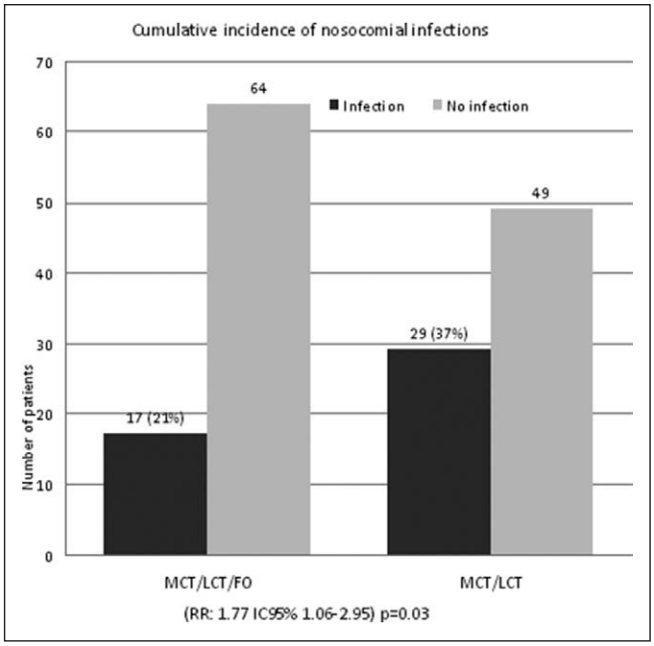

Figure 2. Cumulative prevalence of nosocomial infections. Bar chart showing the number of patients with and without infection in treatment (medium-chain triglyceride [MCT]/long-chain triglycerides [LCT]/fish oil [FO]) and control (MCT/LCT) groups. RR = risk ratio.

significant beneficial effects of n-3 PUFAs administration on relevant clinical outcomes like length of ICU/hospital stay, infection rate, and mortality in critically ill medical patients. This is also reflected by recently published meta-analyses of clinical trials solely performed in this patient population (40, 41). Only one study showed a tendency for reduced length of hospital stay without changes in length of ICU stay (33). Variables shown to be beneficially influenced by n-3 PUFAs are C-reactive protein levels, gas exchange, and reduced need for renal replacement therapy (32, 33, 42). The studies performed so far were restricted to a specific patient group and the number of patients included was small (ranging between 20 and 40 patients), possibly underpowered to detect beneficial effects of n-3 PUFAs administration on clinical outcomes (21).

A recent meta-analysis investigated the effect of n-3 PUFAs administration in a broader defined population of critically ill patients by pooling data from studies performed with surgical and medical ICU patients. This meta-analysis revealed reduced markers of inflammation, improved lung gas exchange, and significantly shorter length of ICU and hospital stay in ICU patients receiving parenteral n-3 PUFAs. Infection rate was lower in the FO-receiving ICU population, but no statistically significant reduction could be shown (22).

The findings of the current study are inconsistent with findings of a large study with 166 medical ICU patients (43). Although, the amount of FO administered was similar (~0.1 g/kg/d) and the same type of lipid emulsion (MCT/LCT, 1:1) was used as control, the authors did not detect any beneficial effect of n-3 PUFAs administration. This might be due to differences in the patient population studied (critically ill medical patients vs critically ill medical and surgical patients) or the duration of FO administration. Although n-3 PUFAs were administered for 7 days in the previous study, patients in the current study received n-3 PUFAs as long as they required PN. It has been reported that levels of free n-3 PUFAs rapidly returned to baseline levels after cessation of infusion (36). Thus, it seems possible that prolonged administration of n-3 PUFAs might be necessary in critical illness to maintain a beneficial n-6/n-3 ratio.

In this study, no statistically significant differences were observed for other clinical outcomes, such as duration of MV, lengths of ICU and hospital stay, and mortality. However, in line with another study (33), length of hospital stay was reduced close to significance in the group that received n-3 PUFAs. Hospital mortality and 6-month mortality were almost equal between groups. A nonsignificant higher mortality was found in the FO group. This is clearly related with a nonhomogeneous distribution of patients with pancreatitis in both groups. Despite there were no significant differences in mortality between both groups, deaths from pancreatitis were more

TABLE 2. Prevalence of Nosocomial Infections

Variable	MCT/LCT, *n* (%)	MCT/LCT/Fish Oil, *n* (%)	*p*
Mechanical ventilation-associated pneumonia[a,b]	14/64 (21.9)	7/67 (10.5)	0.150
Bacteremia[a,c]	12/78 (15.4)	10/81 (12.4)	0.765
Surgical wound infection[a,d]	5/42 (11.9)	4/41 (9.8)	0.936
Intra-abdominal abscess[a,d]	4/42 (9.5)	1/41 (2.4)	0.247
Urinary tract infection[a,c]	3/78 (3.9)	4/81 (4.9)	0.679
Cumulative prevalence[e]	29/78 (37.2)	17/81 (21.0)	0.038
Antibiotic-free days	1.3 ± 2.2	1.7 ± 3.3	0.290

MCT = medium-chain triglyceride, LCT = long-chain triglycerides.
[a]Calculated as (number of infectious episodes)/(patients).
[b]Mechanically ventilated patients only; *n* (MCT/LCT) = 64, *n* (MCT/LCT/Fish Oil [FO]) = 67.
[c]All patients; *n* (MCT/LCT) = 78, *n* (MCT/LCT/FO) = 81.
[d]Surgical patients only; *n* (MCT/LCT) = 42, *n* (MCT/LCT/FO) = 41.
[e]Calculated as (number of patients with nosocomial infection(s))/(number of patients); *n* (MCT/LCT) = 78, *n* (MCT/LCT/FO) = 81.

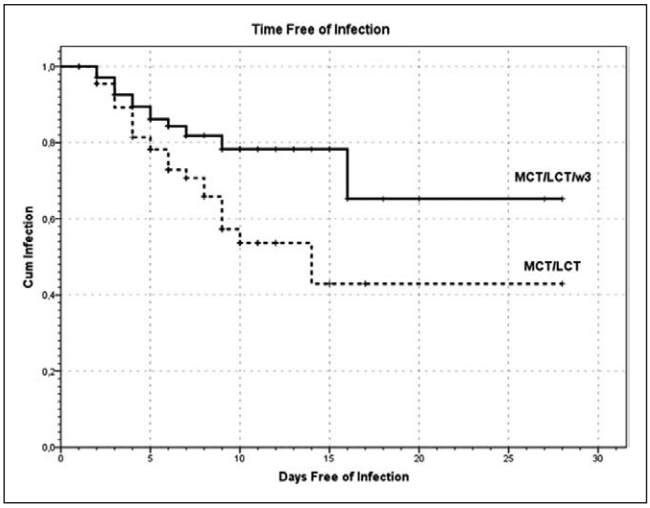

Figure 3. Time free of infection (TFI) in treatment (medium-chain triglyceride [MCT]/long-chain triglycerides [LCT]/fish oil [FO]) and control (MCT/LCT) groups. TFI was estimated for patients without signs of infection on 1st and 2nd days after study enrolment ($n = 68$) for treatment group and ($n = 71$) control group. TFI was significantly longer in the treatment group (21 vs 16 d, $p = 0.03$).

than the 25% mortality in the FO group. Pancreatitis is a complex disease, and the prognosis is more related to the therapeutic approach, particularly the surgical approach, than the effect of any type of nutritional substrates.

In several clinical trials that showed beneficial effects of n-3 PUFAs administration in surgical patients, the control lipid emulsion administered was a pure LCT emulsion, rich in n-6 PUFAs. Thus, one might argue that n-3 PUFAs-enriched lipid emulsions are not immunomodulating but less inflammatory than the control lipid emulsion due to reduced n-6 PUFAs content (40). The findings of the current study with the control lipid being an MCT/LCT emulsion, that is, with reduced n-3 PUFAs content already, indicate that the effects of n-3 PUFAs might indeed be based on immunomodulation. Although no immunologic variables were assessed in the current study, infection rate is a well-established variable in the field of n-3 PUFAs administration on the level of clinical outcomes (22). Thus, previously outlined findings suggest that a modulation of the immune response by n-3 PUFAs underlies the FO-induced reduction of NI prevalence.

ARs recorded did not differ between groups, and no serious or unexpected adverse events were reported confirming the finding of a variety of clinical trials that FO-supplemented PN is safe in critically ill patients (3, 21). Nutritional efficacy was similar with or without FO supplementation.

The recruitment period of the study was longer than expected. This was caused by the difficulties in obtaining informed consent in critically ill patients while having only a short time frame for enrollment since treatment has to be initiated early in the course of critical illness (3). As envisaged in the study protocol, an interim analysis maintaining blinding was performed after recruitment of 175 patients. This interim analysis indicated that the overall prevalence of NIs was lower than assumed for sample-size calculation. This is presumably attributed to the implementation of campaigns such as "Zero Bacteriemia" and "Pneumonia Zero" in Spanish ICUs. Considering the long recruitment period and the finding that sample-size calculation was based on a no longer valid assumption, it was decided to terminate the study. Although the number of patients included into the study was therefore smaller than the sample size estimated in order to set up an adequately powered study able to detect a clinically relevant reduction of the prevalence of NIs by 20%, the number of patients at termination of the study is considered to be acceptable. This consideration is based on the fact that statistically significant results could be detected. Furthermore, the number of patients included is still large compared with the majority of studies available so far.

In conclusion, the study results presented here suggest that administration of ~0.1 g FO/kg BW per day in combination

TABLE 3. Overview of Clinical Outcomes

Clinical Outcome	MCT/LCT ($n = 78$)	MCT/LCT/Fish Oil ($n = 81$)	p
Length of mechanical ventilation (d; median [interquartile range])	8 [8.5]	7 [6.0]	0.470
Length of ICU stay (d; median [interquartile range])	18 [13.25]	12 [18.5]	0.369
Length of hospital stay (d; median [interquartile range])	36.5 [34.0]	25 [34.5]	0.059
ICU mortality (n, %)[a]	16 (20.5)	26 (32.5)	0.106
Patients without pancreatitis	15 (19.2)	19 (23.8)	0.324
Patients with pancreatitis	1 (20.0)	7 (36.8)	0.338
Hospital mortality (n, %)[b]	6 (9.7)	6 (11.1)	1.000
6-month mortality (n, %)[c]	2 (3.6)	2 (4.3)	1.000
6-month survival (Kaplan-Meyer, d)	137.2 ± 7.6	117.7 ± 8.5	0.082

MCT = medium-chain triglyceride, LCT = long-chain triglycerides.
[a]One patient was lost to follow-up: n (MCT/LCT/ fish oil [FO]) = 80.
[b]% of ICU survivors: n (MCT/LCT) = 62, n (MCT/LCT/FO) = 54.
[c]% of hospital survivors, two patients were lost to follow-up for 6-month period: n (MCT/LCT) = 56, n (MCT/LCT/FO) = 46.

TABLE 4. Assessment of Hepatic Dysfunction

Variable	MCT/LCT	MCT/LCT/Fish Oil	*p*
Cholestasis (*n*, %)	66 (84.6)	67 (82.7)	0.832
Liver necrosis (*n*, %)	23 (29.5)	22 (27.2)	0.860
Mixed injury (*n*, %)	44 (56.4)	46 (56.8)	1
Measures taken: no action/retraction/ specific treatment/others (*n*)	51/1/4/4	53/0/4/3	0.920
Alterations concerning PN: none/reduction/ increase/interruption/cessation (*n*)	56/3/0/0/1	57/1/1/1/0	0.619

MCT = medium-chain triglyceride, LCT = long-chain triglycerides.

TABLE 5. Caloric Intake, Lipid, and Protein Intake and Days of Total Parenteral Nutrition and Enteral Nutrition

Variable	MCT/LCT (*n* = 78)	MCT/LCT/FO (*n* = 81)	*p*
Parenteral energy intake (kcal/d)	1,782 ± 312[a]	1,737 ± 353	0.499
Parenteral nitrogen intake (g/d)	17.1 ± 2.1	17.5 ± 2.3	0.231
Protein delivery (g/kg BW/d)	1.41 ± 0.31	1.43 ± 0.11	0.221
Parenteral lipid intake (g/d)	80.0 ± 10.9	79.8 ± 13.1	0.806
Parenteral lipid intake [(g/kg BW)/d]	1.05 ± 0.13	1.04 ± 0.12	0.385
FO intake[b]	0	0.104 ± 0.012	Not done
Days of total PN	8.9 ± 5.4	8.8 ± 6.0	0.574
Initiation of enteral nutrition (*n*)	42	43	0.874
Days of total PN/days of nutritional support (%)	78.0 ± 26.4	78.1 ± 27.4	0.912

MCT = medium-chain triglyceride, LCT = long-chain triglycerides, FO = fish oil, BW = body weight.
[a]For one patient energy intake administered was not registered, *n* = 77.
[b]MCT/LCT/FO lipid emulsion only, FO content: 10%.

with MCT and LCT in a lipid emulsion reduces the risk of NIs and increases the predicted TFIs in critically ill medical and surgical ICU patients. Length of hospital stay was reduced close to significance. The administration of a MCT/LCT/FO parenteral lipid emulsion in critically ill patients was shown to be safe.

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