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Randomized Control Trials

Effect of omega 3 polyunsaturated fatty acids derived from fish oil in major burn patients: A prospective randomized controlled pilot trial

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SUMMARY

Background & aims: The burn patient is the clearest example of prolonged inflammatory response. Various nutrients, particularly omega-3 polyunsaturated fatty acids (ω-3 PUFAs), have been demonstrated as attenuating the inflammatory response, and reduce infectious complications. In absence of definitive evidence in major burns the study aimed at investigating the effect particularly on infectious complications of enteral nutrition enriched with ω-3 PUFAs.

Method: Prospectively randomized controlled trial. Inclusion criteria: adult patients admitted to intensive care (ICU), burns > 15% body surface area (BSA), with inhalation injury requiring mechanical ventilation for ≥ 6 days and enteral nutrition. Intervention: low-fat (18% energy as fat) modular diet (LF-EN) or identical with 50% of fat as fish oil (FO-EN). Study endpoints: infectious and other complications, length of mechanical ventilation time, mortality.

Results: Altogether 92 patients, aged 40 years old and burned 38% BSA were analyzed (45 patients in LF-EN and 47 in FO-EN). Baseline characteristics were similar. Severe sepsis and septic shock together were significantly fewer in FO-EN group, 15% versus 33%, p = 0.03, (others infections unchanged). Non-infectious complications were less frequent in group FO-EN, with a significant reduction of high gastric residual volume (33% versus 8.5%: p = 0.003). Mechanical ventilation was non-significantly shorter with FO-EN (22 versus 26 days). Mortality did not differ.

Conclusion: The inclusion of ω-3 PUFAs in a low fat diet in ICU burned patients was associated with significant clinical benefits compared to a conventional low fat diet, with lower rates of severe sepsis, septic shock and pyloric dysfunction.

Trial identification: NCT02189538.

1. Introduction

Among the critically ill, major burn patients are characterized by the most intense and prolonged inflammatory response. Severe thermal injury is also associated with increased susceptibility to infections, which in turn is linked to increased morbidity and mortality. Infectious complications increase the risk of organ failure, length of intensive care (ICU) and hospital stay.

Nutritional therapy including lipids is essential for these patients survival. Although until recently they were considered exclusively as energy source, some of the fatty acids, and particularly ω-3 PUFAs, eicosapentaenoic acid (EPA) y docosahexaenoic acid (DHA) have shown to have major regulatory roles, specifically to influence the structure and function of cell membranes, eicosanoid metabolism, cytokine production and interaction of regulating the inflammatory immune response [1,2].In addition, feeding high dose of lipids (≥35% of total energy) increases infectious complications [3], while including ω-3 PUFAs in the feeds has shown to decrease infectious complications [4].

This knowledge has led to the addition of ω-3 PUFAs to enteral formulas in combination with other immune-modulating nutrients, such as arginine, glutamine, nucleotides, antioxidants, vitamin E. The combination of various agents has made it difficult to identify which effects could be attributed to each. Besides these diets are even more expensive, reducing their accessibility. In addition burn patients included in the trials have been too few to be able to draw any conclusion [5].

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Based on the available evidence, most of the international nutrition societies, the American Society of Enteral and Parenteral Nutrition (ASPEN) [6], the European Society (ESPEN) [7], and the Canadian guidelines [8] recommended to use ω-3 PUFAs despite some minor differences in formulation. Nevertheless, the choice of the control solutions in the studies which underlies the recommendations (high fat solution) has cast some doubts on the validity of the trials.

Animal trials in the 80s, observed advantages of the decrease in the amount of fat in burn animals' diets [9–11]. Two human trials on this topic in burn patients tend to show that lower fat diets are beneficial regarding infectious complications, without finding any specific impact of fish oil [3,12].

Since 1996, our center (CENAQUE) based on the few available evidences, has been using a locally conditioned low fat modular enteral formula that provides 18% of total calories as fat in the form of sunflower oil rich in ω-6 PUFAs: this low-fat solution constituted our baseline control diet. Our hypothesis is that supplementation with ω-3 PUFAs would improve the outcome of severe burn patients, particularly reducing infectious complications and attenuating the inflammatory response: the study aimed at testing the effect of replacing 50% of the lipids with ω-3 PUFAs derived from fish oil the above endpoints in severely burned patients.

2. Methods

The study was designed as a prospective, randomized double-blind trial of consecutive patients admitted to our ICU between January 2007 and July 2012. The study was conducted after ethical approval of the Center authorities, and with the informed consent of patients or their relatives. The inclusion criteria were: adult patients with burns >15% body surface area (BSA), inhalation injury, requiring mechanical ventilation for ≥6 days, and feeding exclusively by the enteral route for more than ≥6 days. The exclusion criteria were: patients younger than 18 years old, pregnancy or breastfeeding, absence of full commitment for treatment, comorbidity such as HIV, diabetes, cancer, chronic obstructive pulmonary disease, cirrhosis, patients in need of parenteral nutrition, partial parenteral nutrition to achieve caloric goals, patients in need of change in the characteristics of formula, basically carbohydrate content, patients admitted after 24 h post burn, and enteral feeding for less than 6 days. Patients received the intervention all the time that they were with enteral nutrition and were followed until discharge. They were analyzed and compared the evolution in the first 14 days.

2.1. Intervention

The patients were randomized by a simple method by professionals outside the studio at 24 h of their admission to receive either the standard low-fat diet (LF-EN) (sunflower oil) or a low-fat diet in which 50% of the fat was replaced by fish oil rich in ω 3 PUFAs (FO-EN). Blinding: Caregivers (physicians and nurses) and patients were blinded to the composition of the solution. Both diets were similar in consistency and color. The modular diet was prepared in the hospital (Table 1) using fatty acids provided by fish oil VIPEZ® of Landasur Laboratory (Montevideo, Uruguay). Each 100 cc of product, contains, means, EPA, 8 g and DHA 20 g. The cost increases by 0.5 US$ each 1000 Kcal.

2.2. Feeding protocol

Enteral nutrition was started within the first 24 h post burn, through nasogastric tube, continuous drip, with infusion drip in 20 h at a rate of 25 cc/hour advanced every 24 h until energy target was reached. All patients received the same trace element and vitamin supplements (Supradyn, Roche®) (Table 1). No further trace elements were provided due to lack of suitable product in our center. In the absence of calorimetry, the caloric goal was established by the Toronto equation [13] (−4343 + (10.5 × BSA) + (0.23 × intake the previous day) + (0.84 × Harris Benedict basal energy) + (114 × temperature) − (4.5 × days after injury). Fluid and energy balance were calculated daily. Nitrogen balance was performed once a week.

2.3. Clinical management

The resuscitation was based on the Parkland formula, 2–4 ml/Kg/% BSA of ringer lactate. The inhalation injury was diagnosed in all cases by bronchoscopy.

The primary endpoint was infectious complications during the 14 day follow-up period [14,15]: sepsis, bacteremia, respiratory, catheter, wound infections. Sepsis was defined as the "presence of at least 3 of the following criteria: Temperature >39° or <36.5 °C, progressive tachycardia >110 bpm, progressive tachypnea, thrombocytopenia (after day 3) < 100.000/mm^3, hyperglycemia (in the absence of pre-existing diabetes mellitus), a) untreated plasma glucose > 200 mg/dl b) insulin resistance, examples include >7 units/hr. intravenous drip, significant resistance to insulin (>25% increase in insulin requirements over 24 h) inability to continue enteral feeding over 24 h, a) abdominal distension, b) enteral feeding intolerance (residual >150 ml/hr.) uncontrollable diarrhea (>2500 ml/d). It is required a documented infection with at least 1 of the following: cultures positive infection or pathologic tissue source identified or clinical response to antimicrobials.

Severe sepsis, is sepsis as defined above in addition organ dysfunction. Organ dysfunction is defined by presence of the following variables: cardiovascular dysfunction, heart rate ≤120

Table 1
Diet composition for 1000 Kcal.

Components	LowFat-EN	FishOil-EN
Carbohydrates/liter: g/% of energy	154.5/62	154.5/62
Source	Corn maltodextrin	Corn maltodextrin
Protein/liter: g/% of energy	50/20	50/20
Source	Calcium Caseinate	Calcium Caseinate
Fat/liter: g/% of energy	20/18	20/18
Source	Sunflower oil	50% Sunflower oil l 50% Fish oil
Total saturated fatty acid/monounsaturated fatty acid (g)	1.88/5.86	3.18/6.89
Total PUFA-ω 6 (g)/ω 3 (g)	12/0.3	6.34/3.62
Relation PUFA-ω 6 (g)/ω 3 (g)	40:1	1.75:1

Each patient receives daily through multivitamin supplement: Vitamin A, 6666 IU, Vitamin B_1 40 mg, Vitamin B_2 10 mg, Vitamin B_6 20 mg, Folic Acid 2 mg, Vitamin B_{12} 10 μg, Vitamin C 300 mg, Vitamin D_3 1000 IU, Vitamin E 20 mg, Biotin 0.5 mg, Niacin 100 mg, Pantothenic Acid 23.2 mg, Calcium 102.6 mg, Magnesium 42.4 mg, Iron 20 mg, Manganese 1.0 mg, Phosfate 47.6 mg, Copper 2 mg, Zinc 1 mg, Molybdenum 0.2 mg.
Patients also receive daily intake of: Vitamin C 4 g, Vitamin B1 100 mg, Vitamin B6 300 mg, Vitamin K 10 mg and as part of the modular feeding Calcium 840 mg and Phosphorus 414 mg.

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