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The impact of an omega-3 fatty acid rich lipid emulsion on fatty acid profiles in critically ill septic patients

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ABSTRACT

Background: Death from sepsis in the intensive therapy unit (ITU) is frequently preceded by the development of multiple organ failure as a result of uncontrolled inflammation. Treatment with omega-3 (n−3) fatty acids (FAs), principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), has been demonstrated to attenuate the effects of uncontrolled inflammation and may be clinically beneficial in reducing mortality from organ dysfunction. Fish oil (FO) is a source of EPA and DHA.

Methods: A randomized trial investigating the effects of parenteral (intravenous) nutrition providing FO (0.092 g EPA+DHA/kg body weight/day) was conducted. Sixty consecutive ITU patients diagnosed with sepsis were randomised to receive either once daily parenteral FO and standard medical care or standard medical care only.

Results: Forty one patients (21 received fish oil; 20 controls) consented to blood sampling and blood was taken on days 0, 1, 2, 3, 5, 7, 10 and 13; because of deaths, patient discharge and withdrawal of consent, the number of blood samples available for analysis diminished with time. FA composition of plasma phosphatidylcholine (PC), plasma non-esterified FAs (NEFAs) and peripheral blood mononuclear cells (PBMCs) was determined by gas chromatography. EPA and DHA were rapidly incorporated into all 3 lipid pools investigated. There was a reduction in the arachidonic acid (AA) to EPA+DHA ratio in plasma PC and NEFAs. Fewer patients died in the FO group (13.3% (n=4)) compared with the control group (26.7% (n=8)) but this difference was not significant. A reduction in the AA/(EPA+DHA) ratio in PBMCs and plasma PC was associated with significantly improved survival. Plasma PC, plasma NEFA and PBMC FA profiles are rapidly altered by FO infusion in critically ill septic patients.

Conclusion: The provision of high dose n−3 FAs resulted in a rapid and significant increase in EPA and DHA and a reduction in AA/(EPA+DHA) ratio. This latter reduction is associated with improved survival.

1. Introduction

Intensive therapy units (ITUs) will inevitably contain the sickest, most metabolically stressed patients in any care setting. Consequently, mortality rates in ITUs are high, sometimes as high as 60%, despite the improved understanding of the pathophysiology of sepsis [1,2]. Death from sepsis in the ITU is frequently preceded by the development of multiple organ failure as a result of uncontrolled inflammation [3–5]. Sepsis is a serious and complex inflammatory process that is characterised by a systemic inflammatory response to the presence of an infection.

Omega-3 (n−3) fatty acids (FAs), principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown in cell and animal models to have anti-inflammatory effects [6–8]. We recently reported that parenteral administration of n−3 FAs is associated with a significant reduction in organ dysfunction and C-reactive protein (CRP) concentration and may be associated with a reduction in mortality in patients with less severe sepsis [9].

Two recent systematic reviews and meta-analyses have been published investigating the effects of n−3 FAs in the critically ill patient but these did not demonstrate definitively improved outcomes [10,11]. Major confounding factors in the studies analysed included FO being given in differing amounts, as a bolus versus a slow infusion, by different routes (enteral and parenteral) and often in combination with other immuno-modulating nutritional support. In order to optimise the parenteral use of FO for improved

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patient outcome it seems important to understand more about the incorporation of its bioactive fatty acids, EPA and DHA, in ITU patients. Factors such as the timing/duration of parenteral FO and patient factors (such as age and sex) may influence the efficacy of FO and have been hitherto poorly explored.

The aim of this present study was to examine the FA composition of various blood lipid pools in septic patients treated with parenteral FO, to relate these to mortality and to investigate factors that might affect n−3 FA incorporation (age and sex). The lipid pools measured, which are all pertinent to sepsis, were plasma phosphatidylcholine (PC), representing the major phospholipid in the circulation, plasma non-esterified FAs (NEFAs), which represent a direct route of exposure of bioactive fatty acids to cells and tissues, and peripheral blood mononuclear cells (PBMCs), representing cells with a functional role of particular relevance to inflammation, critical illness and sepsis. Thus, our measurements of the FA composition of plasma PC, plasma NEFAs and PBMCs are indicative of the potential of the infused lipid emulsion to modulate cell and tissue function, which in turn may influence clinical course and outcome. It is for this reason that we were interested in the time course of FA composition changes, because it may be desirable in some clinical settings to provide n−3 FAs quickly. The main clinical outcomes from this trial have been published recently [24].

2. Materials and methods

2.1. Study design

The study was performed in a 9-bed general and surgical ITU and a 4-bed general and surgical high dependency unit (HDU) in a single tertiary-referral hospital. The study protocol was reviewed and approved by the National Research Ethics Service (South East Coast Research Ethics Committee (reference number 09/H1102/111)) and the study was conducted in accordance with the Helsinki declaration. From May 2010 until July 2012 sixty consecutive adult patients admitted to the ITU or HDU with sepsis or who developed new sepsis whilst on the ITU for other non-infectious pathologies were prospectively enroled into the study.

Sepsis was defined as a proven or suspected source of infection together with at least two of the four markers of the systemic inflammatory response syndrome (SIRS), namely temperature $>38\,^{\circ}C$ or $<36\,^{\circ}C$, heart rate >90 beats/min, white cell count >12 or $<4\times10^{9}$, or respiratory rate >20 or $PaCO_2<4.2$ kPa. Septic patients were enrolled into the study within 12 h of admission to the ITU or within 12 h of new onset sepsis, as diagnosed by the intensivists. Written informed consent was taken from the patient where possible or from a legal/professional representative if the patient lacked capacity. A 12-h window was allowed for the intensivists to establish a clinical diagnosis of sepsis, to obtain the necessary written consent and to randomise the patients. Patients were randomised using sealed envelopes to receive either standard care or standard care together with infusion of a lipid emulsion based upon FO (Omegaven™; Fresenius Kabi, Bad Homburg, Germany). Full details of the trial methodology may be found elsewhere [9].

2.2. Fish oil infusion

A FO based lipid emulsion (Omegaven™) was given according to the manufacturer's guidelines. Omegaven™ is a 10% lipid emulsion i.e. it contains 100 g lipid/l. The FA component is provided by FO and this comprises 96.3% of the lipid; there is also 2.5 g glycerol/l and 1.2 g egg phospholipid/l. The FA composition of the emulsion is shown in Table 1. Because FO is a natural product, its FA composition can vary and therefore the FA composition of Omegaven™ can vary (see Table 1). We measured the FA composition of a typical batch of Omegaven™ used in the current study and found that it contained 25% of FA as EPA and about 21% as DHA (see Table 1). Omegaven™ was infused daily at 2 ml/kg body weight/day (i.e. 0.2 g lipid/kg body weight/day) at a rate of 0.5 ml/kg/h. Omegaven™ was given daily until day 14 or until death or discharge from the ITU/HDU.

Table 1
Fatty acid composition of Omegaven™.

Fatty acid	Concentration (g/l)	
	As provided by manufacturer	As measured
Myristic acid (14:0)	1.0–6.0	4.5
Palmitic acid (16:0)	2.5–10.0	13.2
Palmitoleic acid (16:1n−7)	3.0–9.0	8.2
Stearic acid (18:0)	0.5–2.0	3.3
Oleic acid (18:n−9)	6.0–13.0	10.6
Linoleic acid (18:2n−6)	1.0–7.0	3.3
Alpha-linolenic acid (18:3n−3)	~2.0	1.2
Arachidonic acid (20:4n−6)	1.0–4.0	1.7
Eicosapentaenoic acid (20:5n−3)	12.5–28.2	25.0
Docosapentaenoic acid (22:5n−3)	1.5–4.5	2.1
Docosahexaenoic acid (22:6n−3)	14.4–30.9	20.8
Total fatty acids	96.3	–

2.3. Blood sampling and plasma and PBMC isolation

Blood samples were collected in all patients on days 0, 1, 2, 3, 5, 7, 10 and 13. In those patients randomised to receive FO, day 0 refers to the time pre parenteral infusion. In addition, two patients consented to 4 hourly blood samples taken over 24 h from the time at which the first FO infusion was commenced for an analysis of the FA response during a single dose of Omegaven™. Blood was collected heparin-coated vacutainers and centrifuged to obtain plasma which was stored at −80°C until analysis. PBMCs were isolated by centrifugation of blood on a density medium gradient (Histopaque-1077; Sigma-Aldrich, Poole, UK) using the manufacturer's instructions and as described in detail elsewhere [12]. PBMCs are a mix of lymphocytes (~85% of cells) and monocytes (~15% of cells) and, using the procedure outlined, are not likely contaminated with other cell types. Samples were stored at −80°C for 3 to 12 months until analysis.

2.4. Fatty acid analysis

PC and NEFAs were isolated from plasma by solid-phase extraction [28]. The FA composition of plasma PC, plasma NEFAs and PBMCs was determined by gas chromatography as described in detail elsewhere [13].

2.5. Clinical data collection

Baseline demographics and clinical data were recorded for 2 weeks or until death or discharge following enrolment in the study. In addition, date of discharge from ITU, discharge from the acute hospital and 28-day mortality were recorded. Microbiological cultures were taken as directed by the intensivists. Patients exited the trial when discharged from the ITU/HDU, at day 14, due to mortality or if they withdrew consent.

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