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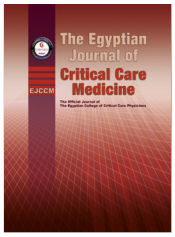

ORIGINAL ARTICLE

Impact of oral omega-3 fatty acids supplementation in early sepsis on clinical outcome and immunomodulation

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KEYWORDS

Omega-3 fatty acid;
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IL6;
PCT

Abstract *Introduction:* Sepsis is a systemic inflammatory response that is usually aggravated by inappropriate immune responses, which can be inhibited by omega-3 fatty acids and antioxidants.

Objectives: To determine the efficacy and safety of omega-3 fatty acid plus antioxidants in early sepsis.

Methods: 75 patients with sepsis were divided equally into: (group A) who received high dose omega-3 fatty acids plus fixed dose antioxidants for consecutive 7 days besides conventional sepsis treatment, (group B) who received the same treatment as group A but a lower dose of omega-3 fatty acids and the control group who received only conventional sepsis treatment. All groups were followed up by: Inflammatory markers, SOFA score monitoring, need for organ supportive measures, length of ICU stay, 28 day mortality, final outcome and complications.

Results: Compared to the control group, the high dose omega-3 fatty acid exhibited significantly lower levels of CRP, IL6 and PCT at day 7 ($P = 0.047$, 0.05, 0.041 respectively). Compared to the control group, group A patients showed significantly lesser need and shorter duration of mechanical ventilation ($P = 0.044$, 0.038 respectively), significantly reduced development of severe sepsis indicated by mean and highest SOFA score; ($P = 0.040$ and 0.046 respectively), with insignificant difference in the need for vasopressors and hemodialysis ($P = 0.12$, 0.6 respectively). Comparing low dose omega-3 fatty acids plus antioxidants group to control group using same parameters, no significant results were found.

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Conclusion: The use of a short term high dose omega-3 therapy is safe and associated with promising effects on inflammatory cascade and may play a role in treatment of these patients.

Introduction

Sepsis, widely accepted as being "the systemic inflammatory response syndrome that occurs after infection, is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual. Inflammation is part of the normal host response to infection and injury. However, excessive or inappropriate inflammation contributes to a range of acute and chronic human diseases and is characterized by the production of inflammatory cytokines, arachidonic acid-derived eicosanoids (prostaglandins, thromboxanes, leukotrienes, and other oxidized derivatives), other inflammatory agents (eg, reactive oxygen species), and adhesion molecules. Thus, basic research and clinical trials have focused on agents capable of blocking steps within the inflammatory cascade [1,2].

However, despite the multitude of therapeutic approaches evaluated, the only inflammation-modulating substances demonstrated to date to benefit patients with severe sepsis are activated protein C and low-dose hydrocortisone [3,4].

Omega-3 fatty acids are essential fatty acids, which are necessary for human health but are not manufactured in the human body and we have to get them through food. They are found in fish, such as salmon, tuna, some plants, and nut oils [5].

Long-chain *n*-3 polyunsaturated fatty acids (PUFAs) decrease the production of inflammatory eicosanoids, cytokines, and reactive oxygen species and the expression of adhesion molecules. Thus, *n*-3 PUFAs are potentially potent anti-inflammatory agents. As such, they may be of therapeutic use in a variety of acute and chronic inflammatory settings. Evidence of their clinical efficacy is reasonably strong in some settings (e.g., in rheumatoid arthritis) but is weak in others (e.g., inflammatory bowel diseases and asthma). More, better designed, and larger trials are required to assess the therapeutic potential of long-chain *n*-3 PUFAs in inflammatory diseases [6].

We aimed in our study to:

- Investigate the anti-inflammatory effects and safety of short-term oral omega-3 fatty acids plus antioxidants as an adjunctive therapy in early sepsis.
- Assess the effect of the use of omega-3 fatty acids plus antioxidants on the progression of the disease to severe sepsis and/or septic shock, and
- Evaluate the impact of this therapy on duration of ICU stay, patient outcome and need for organ supportive measures.

Patients and methods

We prospectively enrolled all patients with early sepsis, admitted to Critical Care Department, Cairo University Hospital; from September 2011 to July 2012. Diagnosis of sepsis was based on clinically suspected infection as per the treating physician or confirmed infection and 2 or more of the following: Temperature $\geqslant 38.3°$or $\leqslant 36$ °C, Heart rate (HR) > 90/min, Respiratory rate (RR) > 20/min or PaCO2 < 32 mmHg, White blood cell count $>12{,}000/mm^3$ or $<4000/m^3$ or >10% immature neutrophils. Early sepsis is defined as sepsis developed within 24 h of the criteria of sepsis. An informed written consent was given by all patients or immediate relative (first degree), and the study protocol was approved by the local Review Board.

Exclusion criteria included:

(1) Age < 18 years.
(2) Significant immunologic suppression (defined as a leukocyte count <5000 cells/mm^3).
(3) Imminence of receiving parenteral nutrition.
(4) Presence of uncontrolled diarrhea.
(5) Recent gastrointestinal bleeding event.
(6) End stage hepatic or renal disease.
(7) Life expectancy less than 24 h.
(8) Significant limitation of survival prognosis (defined as a life expectancy <28 days due to a chronic and/or incurable disease such as uncontrolled cancer or other terminal disease).
(9) Pregnancy.
(10) History of allergy or intolerance to omega-3 FA
(11) Greater than 16 h after meeting inclusion criteria.
(12) Use of omega-3 in the previous weeks.
(13) Patients with severe sepsis, MOD or septic shock on admission.
(14) APACHE II score on admission >25 (predicted mortality >80%).

Patients who met the inclusion criteria were randomized into the study on the day of admission (if they are admitted because of sepsis) or the day they fulfilled the criteria of sepsis (if they acquired sepsis during their ICU stay).

Study protocol

Studied patients were randomized into 3 groups:

High dose omega-3 plus antioxidants group (group A): these patients received the following medications daily for 7 consecutive days either orally or via the nasogastric tube in addition to the conventional treatment for sepsis:

- High doses omega-3 fatty acids (9 g in 3 divided doses) in the form of docosahexaenoic acid and eicosapentaenoic acid (DHA + EPA).
- Antioxidants in the form of ascorbic acid 1000 mg/day, Alpha-tocopherol 400 IU/12 h and selenium 100 μg/day.

Low dose omega-3 plus antioxidants group (group B): these patients received lower doses (3 g omega-3 FA in 3 divided

Table 1 Composition of the enteral diets.

Nutrient	High dose omega-3 F.A.	Low dose omega-3 F.A.	Control group
Protein			
% of total calories	16%	16%	16%
g/day	82	82	82
Carbohydrate			
% of total calories	54%	54%	54%
g/day	265	265	265
Lipid			
% of total calories	30%	30%	30%
g/day	63	63	63
source	14.2% of lipid content were omega-3 FAs 85.8% other fats	4.7% of lipid content were omega-3 FAs 95.3% other fats	0% omega-3FAs 100%other fats

doses plus the same dose of antioxidants daily for 7 consecutive days either orally or via the nasogastric tube) plus conventional sepsis treatment.

Control group (group C): these patients received only conventional sepsis treatment, which consists of treating or eliminating the source of infection, timely and appropriate usage of antimicrobial agents, hemodynamic optimization, and other physiologic organ supportive measures.

The studied population diet was enriched with EPA, DHA, and enhanced levels of antioxidant vitamins, although it remained isocaloric and isonitrogenous to the control diet. The full composition of the 3 groups' diets can be found in Table 1. Patients received enteral nutrition within 6 h of meeting the enrollment criteria. Enteral feeding was delivered at a constant rate to achieve a minimum of 50% basal energy expenditure (BEE; determined using the Harris-Benedict equation) $\times$ 1.3 within the first 24 h. If well tolerated, enteral nutrition was advanced to achieve a minimum of 75% of BEE $\times$ 1.3 within 72 h.

The omega-3 fatty acid supplementation delivered until patients were discharged or until interrupted at physician's discretion or due to the development of any adverse event that could be related to the omega-3 fatty acid.

All patients were followed up for a total of 28 days (4 weeks) from study day 1 or till the day of discharge or death.

Evaluation of patients

All included patients (in all groups) were subjected to the following:

(1) *Full clinical evaluation:* Including history and physical examination with special emphasis on vital signs (BP, HR, Temperature and RR); which were evaluated at the day of admission and then followed daily.
(2) *Laboratory investigations:*
   (a) *Routine labs:* CBC (complete blood count): Hemoglobin, Hematocrit, White blood cells and platelet count. Coagulation profile: PT, PC, INR and PTT. ABGs (arterial blood gases). Liver function tests: ALT (Alanine aminotransferase), AST (Aspartate aminotransferase), BIL (bilirubin) and albumin. Kidney function tests: Na, K, creatinine and urea. These routine labs were withdrawn on study day 1 and subsequently thereafter every day until ICU discharge or demise or up to a total of 28 days.
   (b) *Specific labs for our study:* were done at day 1 then at day 7 (after last dose of omega-3 fatty acids): C-reactive protein (CRP), Procalcitonin (PCT), interleukin-6 (IL-6) and lipid profile: Total cholesterol and triglycerides.

(3) *Microbiological studies:* including pan cultures (sputum, blood, urine or biological fluid according to clinical suspicion) prior to antibiotic administration or after discontinuation of antibiotic for 48 h.
(4) *Imaging studies* required to identify the source of sepsis (e.g. chest X-ray).
(5) *Clinical data:* length of ICU stay, final outcome and need for organ supportive measures (vasopressors, mechanical ventilation and/or hemodialysis) were reported for all patients until ICU discharge or death or up to a total of 28 days.
(6) *Application of scoring systems:* APACHE II score [7,8] and sequential organ failure assessment (SOFA) score [9].

Statistical analysis: Data were statistically described in terms of mean $\pm$ standard deviation ($\pm$SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student's t test for independent samples when comparing 2 groups and one way analysis of variance (ANOVA) test with posthoc 2-group comparisons when comparing more than 2 groups. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is <5. Accuracy was represented using the terms sensitivity, specificity, +ve predictive value, −ve predictive value, over all accuracy. P values < 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

During the time period from September 2011 to July 2012, 75 patients presenting with early sepsis (chest infection in 32 patients, UTI in 8 and soft tissue infection in 35) were enrolled in the study. Patients were randomized into 3 groups (each consists of 25 patients):

(A) *Group A (high dose omega-3 plus antioxidants group):* 25 patients, 10 males and 15 females, with a mean age of 52.8 ± 18.87 presented by early sepsis from a variety of etiologies (12 chest infection, 3 UTI and 10 soft tissue infection).
(B) *Group B (low dose omega-3 plus antioxidants group):* 25 patients, 14 males and 11 females, with a mean age of 53.1 ± 12.47 presented by early sepsis from a variety of etiologies (10 chest infection, 2 UTI and 13 soft tissue infection).
(C) *Group C (control group):* 25 patients, 13 males and 12 females, with a mean age of 50.5 ± 14.77.

Baseline characteristics were comparable in groups A and control regarding age, gender, co morbid conditions (DM, HTN and COPD), and source of sepsis (Table 2).

The anti-inflammatory effect of high dose omega-3 plus fixed dose antioxidants in group A and control group was assessed by serial measurements of the mean level of CRP, IL6, and PCT at predetermined follow up days (study day 1 and 7).

At day 1 they were nearly the same in both groups (*P* value = 0.64, 0.54, 0.59 respectively), while at day 7; there was a statistically significant reduction in group A patients than in controls as regards the mean levels of CRP (39.3 ± 22.9 versus 51.9 ± 14.1, *P* value = 0.047), IL6 (89.4 ± 63 versus 134.9 ± 95.2, *P* value = 0.05) and PCT (0.98 ± 0.72 versus 1.46 ± 0.57, *P* value = 0.041) (Table 3).

The mean level of TG at day 1 was nearly the same in groups A and control [123.9 ± 39.3 for group A versus 107.8 ± 41.1 for control, *P*-value = 0.146] and at day 7; there was insignificant difference between group A and control (120.3 ± 40.3 versus 106.9 ± 41.9, *P* value = 0.169).

The effect of high dose omega-3 plus fixed dose antioxidants (group A) on clinical course was determined by the need for organ supportive measures (vasopressors, mechanical ventilation and need for acute hemodialysis). Comparing both groups we found that group A exhibited significantly lower need for mechanical ventilation (*P* value = 0.044). However, there were insignificant differences in the need for vasopressors (*P* value = 0.123) and for acute hemodialysis (*P* value = 0.63) (Fig. 1).

There was an insignificant difference between group A and control as regards the mean length of ICU stay (11.6 ± 6.1 in group A versus 13.9 ± 4.2 in controls, *P*-value = 0.124) and the 28 day mortality (32% versus 40%, *P* value = 0.56). But there was a statistically significant reduction of the duration of mechanical ventilation in group A patients when compared with controls (6.7 ± 3.8 days versus 10.9 ± 6.2 days, *P*-value = 0.038) (Table 4).

The severity of illness during ICU stays in both group A and control was evaluated in each patient in the two groups at admission (initial SOFA) and serially every day by using sequential organ failure assessment (SOFA) score then the mean and highest values were determined. The initial SOFA score on admission; showed no significant difference (*P* value = 0.78). But during the hospital course there was significant difference between the two groups in favor of group A, as indicated by mean SOFA score (*P*-value = 0.040) and highest score (*P* value = 0.046) (Table 5).

There was a nonsignificant difference between group A and control as regards the incidence of diarrhea (20% versus 16%, *P* value = 0.8) or the incidence of bleeding (16% versus 12%, *P* value = 0.76).

Comparing low dose omega-3 fatty acids plus antioxidants group (group B) to control as regards the previous measurements; no significant results were found (Table 6–8).

Table 3 Comparison between group A and control as regards the CRP, PCT and IL6 levels at day 1 and day 7.

	Group A	Control	*P*-value
CRP at day1(mg/l)	55.9 ± 32.8	53.1 ± 26.6	0.64
CRP at day 7	39.3 ± 22.9	51.9 ± 14.1	0.047
PCT day1 (ng/ml)	1.36 ± 0.39	1.39 ± 0.43	0.59
PCT day 7	0.98 ± 0.72	1.46 ± 0.57	0.041
IL6 day1	136.5 ± 75	138.2 ± 80.7	0.71
IL6 day 7	89.4 ± 63	134.9 ± 95.2	0.05

Table 2 Age, gender, comorbidity and source of sepsis of group A and control.

	Group A (*n* = 25)	Control (*n* = 25)	*P*-value
Age	52.8 ± 18.87	50.5 ± 14.77	0.68
Gender			
Males	10 (40%)	13 (52%)	0.37
Females	15 (60%)	12 (48%)	0.42
Comorbidites			
Diabetes	12 (48%)	15(60%)	0.56
Hypertension	13 (52%)	12 (48%)	0.77
COPD	9 (36%)	11 (44%)	0.46
Source of sepsis			
Chest infection	12 (48%)	10 (40%)	0.53
UTI	3 (12%)	3 (12%)	1
Soft tissue infection	10 (40%)	12(48%)	0.53

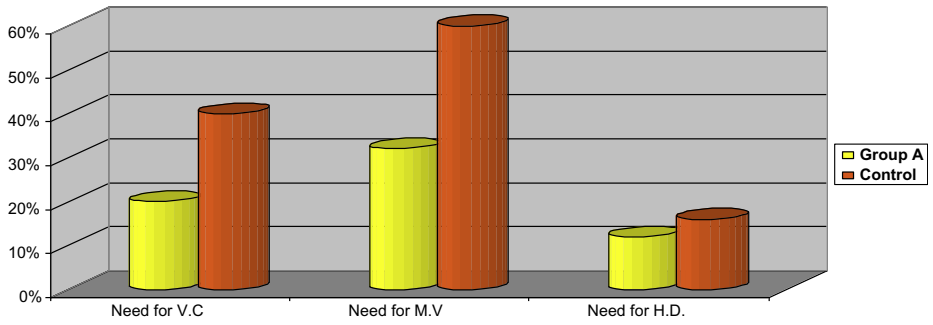

Figure 1 The need for organ supportive measures in group A and control.

Table 4 Comparison between group A and control as regards the length of ICU stay, duration of mechanical ventilation and 28 day mortality.

	Group A	Control	*P*-value
Length of ICU stay (days)	11.6 ± 6.1	13.9 ± 4.2	0.124
Duration of mechanical ventilation (days)	6.7 ± 3.83	10.9 ± 6.3	0.038
28 day mortality	8 (32%)	10 (40%)	0.56

Table 5 Comparison between group A and control as regards the initial SOFA, mean SOFA, and highest SOFA scores in both groups.

	Group A	Control	*P*-value
Initial SOFA (on admission)	3.7 ± 0.96	3.6 ± 0.87	0.78
Mean SOFA (on treatment)	3.7 ± 1.2	4.9 ± 3.3	0.040
Highest SOFA (on treatment)	5.1 ± 2.8	7.5 ± 4.6	0.046

Table 6 Comparison between group B and control as regards the CRP, PCT and IL6 levels at day 1 and day 7.

	Group B	Control	*P*-value
CRP at day1 (mg/l)	52.4 ± 44	53.1 ± 26.6	0.75
CRP at day 7	47.4 ± 26	51.9 ± 14.1	0.58
PCT day1 (ng/ml)	1.37 ± 0.44	1.39 ± 0.43	0.86
PCT day 7	1.26 ± 0.91	1.46 ± 0.57	0.43
IL6 day1	136.9 ± 71.4	138.2 ± 80.7	0.81
IL6 day 7	106.8 ± 93.8	134.9 ± 95.2	0.28

Discussion

Currently available strategies for the management of sepsis focus on the severe forms of the disease (e.g septic shock), which is always associated with elevated death risk [10,11]. Some researchers showed that omega-3 fatty acids could reduce inflammation and may help lower the risk of chronic diseases such as heart disease, cancer, and arthritis. They are found in fish oils and can decrease the production of inflammatory eicosanoids, reactive oxygen species and the expression of adhesion molecules [6].

We had examined the anti-inflammatory effect of omega-3 fatty acids combined with antioxidants in humans as guided by measuring serum levels of CRP, PCT and IL6 at study day 1 and day 7 which reflects the effect of high dose omega-3 fatty acids combined with antioxidants on drivers of sepsis.

In the current study we found that the mean level of CRP, IL6 and PCT at day 1 was nearly the same in both group A and control which was elevated above the normal range, possible due to sepsis. The mean level of CRP, IL6 and PCT at day 7 was significantly reduced in group A compared to control (*P* value = 0.047, 0.05, 0.041 respectively). In concordance with our study Farzaneh-Far et al. (2009) proved that

Table 8 Comparison between group B and control as regards the initial SOFA, mean SOFA, and highest SOFA scores in both groups.

	Group B	Control	*P*-value
Initial SOFA (on admission)	3.3 ± 1.31	3.6 ± 0.87	0.51
Mean SOFA (on treatment)	4.6 ± 3.1	4.9 ± 3.3	0.77
Highest SOFA (on treatment)	6.4 ± 4.8	7.5 ± 4.6	0.59

Table 7 Comparison between group B and control as regards the length of ICU stay, duration of mechanical ventilation and 28 day mortality.

	Group B	Control	*P*-value
Length of ICU stay (days)	13.6 ± 4.1	13.9 ± 4.2	0.94
Duration of mechanical ventilation (days)	8.5 ± 4.63	10.9 ± 6.3	0.29
28 day mortality	11 (44%)	10 (40%)	0.76

among patients with stable coronary artery disease (CAD), levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in erythrocyte membrane lipids were inversely associated with CRP and IL-6. The inverse association of ω-3 fatty acids with CRP and IL-6 was not modified by multiple variables, including statin use [12]. Also Kalogeropoulos et al. (2010) similarly in the ATTICA study in Greece found that total plasma ω-3 fatty acids were inversely associated with CRP, IL-6, and TNF-α. [13]. Contrary to these data Tayyebi-Khosroshahi et al. (2012) had demonstrated in a randomized controlled trial performed on 37 patients with end-stage renal disease undergoing dialysis, that omega-3 fatty acids supplementation (3 g per day for 2 month) significantly decreased the serum levels of TNF-α, however the difference noted in CRP before and after supplementation was not statistically significant (P > 0.05) [14].

In the current study we had examined the effect of early high dose omega-3 plus antioxidants therapy on reducing the degree of severe sepsis and noticed a diminished risk of development of severe sepsis as indicated by comparing SOFA score and clinical course during ICU stay as follows: On comparing the initial SOFA scores between the group A and control on admission; our data showed no significant difference (*P* value = 0.78). During the hospital course there was significant difference between both groups in favor of group A, as indicated by mean SOFA (*P*-value = 0.04) and highest SOFA (*P* value = 0.04). Our results are in agreement with Pontes-Arruda et al [15] who proved that enteral nutrition with EPA/GLA and elevated antioxidants, when used in the early stages of sepsis in patients without any organ failure and in need of enteral nutrition, can play a beneficial role by slowing the progression of the disease to severe sepsis and septic shock but it was not possible to report changes of SOFA scores, as the trial was not designed to collect daily SOFA scores [15].

Comparing group A and controls; group A exhibited significant decrease in need for mechanical ventilation (*P* value = 0.04); but on the other hand there was a nonsignificant decrease in the need for vasopressors (*P* value = 0.12) and acute hemodialysis (*P* value = 0.5).

Similar to our data, Pontes-Arruda et al [15] used enteral nutrition with eicosapentaenoic acid (EPA), g-linolenic acid (GLA) and antioxidants in the early treatment of sepsis in a multicenter, prospective, randomized, double-blinded, controlled study (the INTERSEPT study). Data analysis demonstrated that patients fed the EPA/GLA diet developed less severe sepsis and/or septic shock than patients fed the control diet (26.3% versus 50%, respectively; *P* = 0.026). The patients in the study group also had shown incidence of cardiovascular failure (21% versus 36.2%, respectively; *P* = 0.038) and respiratory failure (24.6% versus 39.6%, respectively; *P* = 0.036) compared to the control group. The percentage of patients fed the EPA/GLA diet requiring invasive mechanical ventilation was reduced compared to controls (18.9% versus 33.9%, respectively; *P* = 0.394) [15].

On the other hand Rice et al (2011) in a randomized, double-blind, placebo-controlled, multicenter trial on 272 adults who developed acute lung injury and required mechanical ventilation; found that twice-daily enteral supplementation of *n*-3 fatty acids, γ-linolenic acid, and antioxidants did not improve the primary end point of ventilator-free days or other clinical outcomes in patients with acute lung injury and may be harmful. Despite an 8-fold increase in plasma eicosapentaenoic acid levels, patients receiving the *n*-3 supplement had fewer ventilator-free days (14.0 versus 17.2; *P* = 0.02) and intensive care unit-free days (14.0 versus 16.7; *P* = .04)). Patients in the *n*-3 fatty acids group also had fewer nonpulmonary organ failure–free days (12.3 versus 15.5; *P* = 0.02) [16].

Regarding the length of stay in the ICU, we found that group A exhibited a non significant reduction in the length of ICU stay. The mean length of stay in the ICU was 11.6 ± 6.1 days for group A versus 13.9 ± 4.2 days for the control group (*P*-value = 0.124).

In accordance with our results, Barbosa et al. (2010) found that "Inclusion of fish oil in parenteral nutrition provided to septic ICU patients increase plasma eicosapentaenoic acid, modifies inflammatory cytokine concentrations and improves gas exchange. These changes are associated with a tendency toward shorter length of hospital stay". In this study they investigated the effects of parenteral fish oil on plasma phospholipid fatty acids, inflammatory mediators, and clinical outcomes on 25 patients with systemic inflammatory response syndrome or sepsis, and predicted the need for parenteral nutrition. The results showed the following: Plasma interleukin (IL)-6 concentration decreased significantly more, and IL-10 significantly less, in the fish oil group (both *P* < 0.001). At day 6 the ratio PO2/FiO2 was significantly higher in the fish oil group (*P* = 0.047) and there were fewer patients with PO2/FiO2 < 200 and < 300 in the fish oil group (*P* = 0.001 and *P* = 0.015, respectively). However days of mechanical ventilation, length of intensive care unit (ICU) stay and mortality were not different between the two groups [17].

Lorenzo et al (2012) in randomized controlled trials comparing *n*-3 PUFA-enriched lipid emulsions with standard non-enriched lipid emulsions in surgical and ICU patients receiving parenteral nutrition [A total of 23 studies (*n* = 1502 patients: *n* = 762 admitted to the ICU) were included]; found no statistically significant difference in mortality rate between patients receiving *n*-3 PUFA-enriched lipid emulsions and those receiving standard lipid emulsions. However, *n*-3 PUFA-enriched emulsions are associated with a statistically and clinically significant reduction in the infection rate and the lengths of stay, both in the ICU and in hospital overall [18].

In the current study we had examined the effect of early high dose omega-3 plus antioxidants therapy on duration of mechanical ventillation (days). The mean duration of mechanical ventillation (days) was 6.7 ± 3.8 days in group A versus 10.9 ± 6.2 days in the control (*P*-value = 0.038); which signifies a statistically significant reduction in the duration of mechanical ventillation (days). In concordance with our results Singer et al. (2006) performed a randomized trial on 100 artificially ventilated patients admitted in ICU with ARDS or ALI, half of them enterally received a diet enriched with eicosapentaenoic acid and gamma-linolenic acid. Major goals of M.V were to reach oxygen saturation above 90%, peak airway pressure lower than 35 cm H_2O and a tidal volume of less than 7 ml/kg. The levels of PEEP and of fi_{O2} were adjusted to meet these objectives. Compared with their baseline, the treatment group demonstrated increases in oxygenation on days 4 and 7, which were greater than those in the control group in a statistically significant manner. The fish oil group also did better regarding improvement in lung compliance. There was also a significant difference in the length of ventilation days as compared with the treatment group, but there were no significant

differences in the length of ICU/hospital stay and mortality between the two groups [19].

Regarding the complications of high dose omega-3 plus antioxidants therapy diarrhea was more in group A (20%) compared to the control group (16%); however this difference was not statistically significant (P value = 0.8). In agreement with these data Pontes-Arruda et al. found that no statistical difference between studied patients and control in the incidence of diarrhea [16]. Opposite to that Rice et al. in their study found that the use of the n-3 supplement resulted in more days with diarrhea in the studied group than the control (29% versus 21%; P = 0.001) [16].

There was a statistically nonsignificant reduction in 28 day mortality in (group A) 32% compared to the control group 36%; however this difference was not statistically significant (P value = 0.26). According to Pontes-Arruda et al. no significant differences in 28-day all-cause mortality were observed (26.2% EPA/GLA diet versus 27.6% control diet, respectively; P = 0.72). [16] Also Rice et al. found that 60-day hospital mortality was 26.6% in the n-3 group versus 16.3% in the control group (P = 0.05). [16].

High dose omega-3 plus antioxidants (group A) in our study were significantly effective in reducing the inflammatory markers and improving the chest condition which was not found when a smaller dose (group B) had been used. In accordance with our results Helle et al. in their study evaluated dose-dependent effects of parenteral supplementation of a 10% fish oil emulsion on diagnosis- and organ failure-related outcome in a total of 661 patients receiving total parenteral nutrition for $\geqslant$3 days. The primary study end point was survival; secondary end points were length of hospital stay and the use of antibiotics with respect to the primary diagnosis and the extent of organ failure. The patients enrolled in this survey were with a body mass index of 25.1 ± 4.2 and simplified Acute Physiology Score (SAPS) II score of 32.2 ± 13.6. Length of hospital stay was 29.1 ± 18.7 days (12.5 ± 14.8 days in the ICU). Total parenteral nutrition, including fish oil (mean, 0.11 g/kg/day) administered for 8.7 ± 7.5 days lowered hospital mortality from 18.9% to 12.0% (p < 0.001). The fish oil dose kg/day did correlate with beneficial outcome (intensive care unit stay, hospital stay, mortality). Fish oil had the most favorable effects on survival, infection rates, and length of stay when administered in doses between 0.1 and 0.2 g/kg/day. Lower antibiotic demand by 26% was observed when doses of 0.15–0.2 g/kg/day were used as compared with doses of < 0.05 g/kg/day. [20] Also Murakami et al. proved that among young Japanese women, the protective effect of ω-3 PUFAs against HS-CRP elevation was found only when ω-3 PUFAs supplied greater than 1.1% of dietary calories [21].

Conclusion

The use of short term high dose omega-3 fatty acids plus antioxidant therapy in patients with early sepsis without associated organ dysfunction seems to be safe and associated with promising effects on inflammatory cascade and may play a beneficial role in the treatment of these patients by contributing to slowing the progression of sepsis-related organ dysfunction, especially with regard to respiratory dysfunction. However, it did not affect the 28 day mortality.

Recommendations:

- We recommend using short term high dose omega-3 fatty acids plus antioxidants therapy as an adjunctive line of treatment in early sepsis.
- Undertake further studies with greater number of patients to study the effect of longer-term treatment regimen on early sepsis.
- Study the impact of omega-3 fatty acids therapy on severe sepsis and septic shock.

Conflict of interest

The authors declare that they have no competing interests or any conflicts with any authority.

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