

JOURNAL CLUB CRITIQUE

ω-3 fatty acids, γ-linolenic acid, and antioxidants: immunomodulators or inert dietary supplements?

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Expanded abstract
Citation

Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P. Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury. *JAMA*. 2011; 306(14):1574-1581. PubMed PMID: 21976613.

Background

The omega-3 (n-3) fatty acids docosahexaenoic acid and eicosapentaenoic acid, along with γ-linolenic acid and antioxidants, may modulate systemic inflammatory response and improve oxygenation and outcomes in patients with acute lung injury.

Methods

Objective: To determine if dietary supplementation of these substances to patients with acute lung injury would increase ventilator-free days to study day 28.

Design: The OMEGA study, a randomized, doubleblind, placebo-controlled, multicenter trial conducted from January 2, 2008, through February 21, 2009. All participants had complete follow-up.

Setting: This trial occurred at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network.

Subjects: Participants were 272 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition.

Intervention: Twice-daily enteral supplementation of n-3 fatty acids, γ-linolenic acid, and antioxidants compared with an isocaloric control. Enteral nutrition, directed by a protocol, was delivered separately from the study supplement.

Outcomes: Ventilator-free days to study day 28.

Results

The study was stopped early for futility after 143 and 129 patients were enrolled in the n-3 and control groups. Despite an 8-fold increase in plasma eicosapentaenoic acid levels, patients receiving the n-3 supplement had fewer ventilator-free days (14.0 vs 17.2; $P=.02$) (difference, -3.2 [95% CI, -5.8 to -0.7]) and intensive care unit-free days (14.0 vs 16.7; $P=.04$). Patients in the n-3 group also had fewer nonpulmonary organ failure-free days (12.3 vs 15.5; $P=.02$). Sixty-day hospital mortality was 26.6% in the n-3 group vs 16.3% in the control group ($P=.054$), and adjusted 60-day mortality was 25.1% and 17.6% in the n-3 and control groups, respectively ($P=.11$). Use of the n-3 supplement resulted in more days with diarrhea (29% vs 21%; $P=.001$).

Conclusions

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.

Commentary

Interest in the use of immunomodulation through nutrition for patients with Acute Lung Injury (ALI) came to attention after a 1999 article by Gadek et al demonstrated an increase in 28-day ventilator free days (VFD), reduction of intensive care unit (ICU) length of stay and new organ failure when enteral diets were supplemented with omega-3 fatty acid, γ-linolenic acid (GLA), and antioxidants¹. Subsequent studies have had similar findings. A 2006 study by Pontes-Arruda et al. demonstrated a similar increase in VFDs, increase in ICU free days as well as a reported 19% absolute reduction in mortality with the use of the same enteral supplements². Another study in 2006, by Singer and colleagues, found an increase in oxygenation through this supplementation, but no change in ICU length of stay, VFDs or mortality³. These three studies became the basis of a meta-analysis

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on the subject as well as the justification to provide a Grade A level recommendation by the Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) to endorse the use of these enteral supplements in patients with ALI^{4,5,6}.

OMEGA sought to evaluate the primary endpoint of VFDs at 28 days through bolus supplementation of omega-3 fatty acids, GLA and antioxidants compared to no immunomodulation supplementation. OMEGA was a trial performed concurrently in a 2x2 factorial distribution with EDEN, a trial to assess differences in full versus trophic enteral nutrition in patients with ALI. Patients in the OMEGA trial were randomized to receive twice daily supplementation or an iso-caloric control compound in addition to their baseline enteral nutrition. Using an intent-to-treat analysis, their results demonstrate a statistically significant decrease in VFDs compared with the control arm as well as a trend toward increased mortality. Their results also did not demonstrate any clinically or statistically significant improvement in pulmonary function or physiology on ventilator support. This prompted the study's data and safety monitoring board (DSMB) to stop the trial early for futility.

Although the study was ended early, it did provide significant findings in terms of enteral immunomodulation in the treatment of ALI. One of this study's greatest strengths is its size. OMEGA was able to recruit and randomize 272 patients, compared to the 165 patients or fewer in each of the prior three studies, making it the largest to evaluate an effect of enteral immunomodulation on ALI. Another significant strength of this study was the ability to demonstrate the biologic effects of omega-3 fatty acids, GLA and antioxidants. They demonstrate (Figure 2 and efigure 2a, 2b) that serum levels of eicosapentaenoic acid did rise, but there was no change in the serum levels of measured inflammatory mediators, interleukins (IL) 6 and 8. The destination of these substances could be accounted for by a rise in urinary concentrations. Additionally, a 2x2 factorial analysis was performed to demonstrate no interaction between these arms of the study and those involved in the EDEN component ($p=0.47$).

This was a well done study without many weaknesses. There was no benefit from enteral supplementation with omega-3 fatty acids, GLA and antioxidants, but there was statistical significance for decreased VFDs opposing the results from previously conducted studies. Another potential weakness is that this trial utilized bolus dosing opposed to continuous supplementation that was utilized in prior studies on the effects of omega-3 fatty acids, GLA and antioxidants on ALI. Finally, the enriched supplement appears to have a different composition (when converted to equivalent units of measurement)

than the omega-3 fatty acids, GLA and antioxidants utilized in prior studies. These points are not direct weakness inherent in this trial's design, but rather limits external validation to previous studies.

The results of this study raise enough attention to question the foundations of the A.S.P.E.N. grade A recommendations to utilize enteral nutrition with omega-3 fatty acids, GLA and antioxidants in ALI. The strengths of this study are enough to reconsider practice guidelines to endorse their use in the treatment of ALI. While the idea of using enteral nutrition to modulate the immune seemed promising, other studies have subsequently showed little benefit, ranging from cardiovascular events, glycemic control or rates of infectious complications in critically ill patients as well as the primary care setting^{7,8}. The authors of the OMEGA study suggest that the changes seen in this trial, compared to the prior studies on the use of omega-3 fatty acids, GLA and antioxidants in ALI may have been the result of changes in non-experimental covariates, such as increased attention to fluid management and lung-protective ventilation, as a result of the ARDSnet trials. Although omega-3 fatty acids, GLA and antioxidants substances appear to have good bioavailability, their physiologic effects seem to be more as inert substrates than modifiers of inflammation as measured by this trial.

Recommendation

Although this study was ended early for futility to decrease VFDs through enteral supplementation with omega-3 fatty acids, GLA and antioxidants, it also raises concern for the potential for increased mortality. Moreover, it is rare that a single study greatly change practice patterns. The strongest conclusion made from this article is that these substrates do not decrease ventilator free days. Consequently, this article has enough merits to warrant a revision in the current guidelines which provide a grade A level recommendation to endorse the use of enteral omega-3 fatty acids, GLA and antioxidants in the treatment of ALI.

Competing interests

The authors declare that they have no competing interests.

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