Enteral Omega-3 Fatty Acid, γ-Linolenic Acid, and Antioxidant Supplementation in Acute Lung Injury

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**Context** 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.

**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, Setting, and Participants** The OMEGA study, a randomized, double-blind, placebo-controlled, multicenter trial conducted from January 2, 2008, through February 21, 2009. Participants were 272 adults within 48 hours of developing acute lung injury requiring mechanical ventilation whose physicians intended to start enteral nutrition at 44 hospitals in the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. All participants had complete follow-up.

**Interventions** 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.

**Main Outcome Measure** 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.

**Trial Registration** clinicaltrials.gov Identifier: NCT00609180

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established ALI have n-3 levels as low as 6% of normal, suggesting a potential role for n-3 dietary supplementation in patients with ALI. Preclinical data indicate that the n-6 γ-linolenic acid (GLA), in conjunction with the n-3 fatty acid EPA, reduces neutrophil leukotriene synthesis and stimulates production of the vasodilator prosta
glandin E₁, which also may be beneficial in ALI. ¹⁰,¹¹

Three randomized controlled studies, conducted in patients with ALI or sepsis-induced respiratory failure, demons
trated an association between the administration of an enteral formula en
riched in n-3 fatty acids, GLA, and antioxidants and improved oxygenation and respiratory physiology compared
with an unenriched, high-fat for-
ti
toxin.

Table 1. Daily Nutrients in Omega-3 (n-3) vs Control Supplements

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>n-3 (240 mL)</th>
<th>Control (240 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, kcal</td>
<td>480</td>
<td>474</td>
</tr>
<tr>
<td>Protein, g</td>
<td>3.8</td>
<td>20</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>4.2</td>
<td>51.8</td>
</tr>
<tr>
<td>Fat, g</td>
<td>44.6</td>
<td>22</td>
</tr>
<tr>
<td>EPA</td>
<td>6.84</td>
<td>0</td>
</tr>
<tr>
<td>DHA</td>
<td>3.40</td>
<td>0</td>
</tr>
<tr>
<td>GLA</td>
<td>5.92</td>
<td>0</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>1000</td>
<td>76</td>
</tr>
<tr>
<td>All-natural vitamin E, IU</td>
<td>440</td>
<td>12</td>
</tr>
<tr>
<td>Beta-carotene, mg</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>Zinc, mg</td>
<td>24.2</td>
<td>5.8</td>
</tr>
<tr>
<td>Selenium, µg</td>
<td>85.2</td>
<td>18</td>
</tr>
<tr>
<td>L-Carnitine, mg</td>
<td>180</td>
<td>38</td>
</tr>
<tr>
<td>Taurine, mg</td>
<td>350</td>
<td>138</td>
</tr>
</tbody>
</table>

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GLA, γ-linolenic acid.

GLA, and antioxidants would in
crease the ratio of n-3 to n-6 fatty ac
cids, reduce inflammatory mediators,
and improve the primary outcome of
ventilator-free days and other clinical
outcomes in patients with ALI.

METHODS

The trial was approved by the institutional review board at each of the 44 en
rrolling hospitals of the National Heart, Lung, and Blood Institute ARDS Clinical Trials Network, listed at the end of
this article. Written informed consent
was obtained from every patient or sur
rogate prior to any study procedure. De
tails of the methods are available in the
eMethods.

Patients

Patients with ALI requiring mecha
nical ventilation whose physicians in
tended to start enteral nutrition were
eligible for inclusion. Specifically, pa
tients had to be receiving mechanical
ventilation, have a ratio of partial pres
ture of arterial oxygen (PaO₂) to frac
tion of inspired oxygen (FiO₂) of less
than 300 (adjusted if altitude ex
cceeded 1000 m), and have bilateral pul
monary infiltrates consistent with edema on chest radiograph without
clinical evidence of left atrial hyperten
sion. The most frequent exclusion cri
tera are shown in Figure 1 (full ex
clusion criteria are available in the
eMethods, available at http://www.jama
.com). Patients were stratified by hos
pital and the presence of shock at base
line and then randomized via a cen
tralized Web-based system to re
ceive either twice-daily enteral supple
mentation of n-3 fatty acids, GLA, and
antioxidants (n-3 supplement) or an
isocaloric-isovolemic carbohydrate
rich control (TABLE 1). Participants
were also simultaneously randomized
to a separate ongoing trial (the EDEN
study) comparing low- vs full-calorie
enteral nutrition in a 2 × 2 factorial de
sign. Per National Institutes of Health
protocol, race and ethnicity were col
lected from administrative data using
census definitions.
Study Procedures
The n-3 or control supplement was administered enterally as twice-daily boluses of 120 mL beginning within 6 hours of randomization. The isocaloric-isovolemic control was identical in appearance and smell to the deodorized n-3 supplement. Dosing continued until the earliest of 21 days, 48 hours of unassisted breathing, or extubation. The energy provided by the boluses supplemented that provided by each primary physician’s choice of standard continuous non–n-3-enriched enteral formula. The rate of continuous enteral feeding was managed by a protocol with an algorithm for gastrointestinal intolerances (eMethods). The supplement was administered even if enteral nutrition was interrupted, as long as the patient was tolerating enteral medications.

Patient care was managed according to simplified versions of the lung protective ventilation and fluid-conservative hemodynamic management protocols used in previous ARDS Network trials (eMethods).6,12 Institution-specific insulin protocols were used to target blood glucose ranges of 80 to 150 mg/dL (to convert to mmol/L, multiply by 0.0555), with tighter control allowed per local usual practice. Patients were maintained in the semirecumbent position to decrease the risk of aspiration and nosocomial pneumonia.18

Primary and Secondary End Points
The primary end point of this study was ventilator-free days (VFDs), defined as the number of days alive and breathing without assistance from randomization to day 28. VFDs were counted only for the final period of unassisted breathing in patients who required more than 1 episode of assisted breathing through day 28. Patients who died before day 28 were assigned zero VFDs.

Secondary end points included 60-day mortality before hospital discharge with unassisted breathing, number of ICU- and organ failure–free days, frequency of gastrointestinal intolerance, plasma levels of IL-6 and IL-8 on days 3 and 6, urinary levels of series 4 and 5 leukotrienes on day 6 (eMethods), and development of new infections. Patients alive in the hospital at day 60 were considered to have survived. Selected plasma fatty acid levels were measured at baseline and days 3, 6, and 12 (eMethods).

Statistical Analysis
With a maximum enrollment of 1000 patients and 4 planned interim analyses, the study had statistical power of 90.7% to detect a 2.25-day increase in VFDs, assuming a mean of 14 VFDs and standard deviation of 10.5. The study was monitored using a group sequential design with asymmetric stopping boundaries for efficacy and futility designed using alpha and beta spending boundaries (eMethods).19 An independent data and safety monitoring board (DSMB) conducted an analysis of serum n-3 levels after enrollment of the first 60 patients, a safety analysis after enrollment of 100 patients, and an interim analysis after enrollment of 272 patients. Although VFDs was the primary end point, the DSMB was advised to consider mortality in their decision to stop the trial for either efficacy or futility.

Means and standard deviations are reported for baseline continuous variables, and counts and percentages are reported for baseline categorical variables, with differences assessed using t tests and χ² tests, respectively. Plasma levels of IL-6, IL-8, leukotrienes, and urinary isoprostanes were log transformed and compared using analysis of variance with baseline levels as covariates. Categorical outcome variables are reported as percentages with 95% confidence intervals. The continuous outcome variables (VFDs, ICU-free days, and organ failure–free days) are reported as means and standard deviations, with differences assessed using analysis of variance controlling for baseline shock and enrollment group of the EDEN study.

Logistic regression controlling for baseline shock and randomization group of the EDEN study was used to analyze mortality. Adjusted mortality rates were calculated using 7 baseline mortality-predicting covariates derived from a previous study of similar

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populations: age, Acute Physiology and Chronic Health Evaluation III (APACHE III) score, plateau pressure, missing plateau pressure, number of organ failures, and the alveolar-arterial difference in PaO₂ value. Proportion curves over time were plotted for survival and unassisted breathing.

All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina) on an intention-to-treat basis, with 2-sided P ≤ .05 considered significant. P values were not corrected for multiple comparisons or early stopping.

RESULTS

The study was stopped by the DSMB for futility at the first interim analysis after 143 patients had been randomized to receive the n-3 supplement and 129 to receive the isocaloric control. Severe chronic lung disease, ALI present greater than 48 hours, mechanical ventilation for longer than 72 hours, and inability to obtain consent were the most frequent exclusions (Figure 1). All patients had complete follow-up to the earlier of hospital discharge or day 60.

Study Supplement Pharmacokinetics and Pharmacodynamics

Daily calories provided by enteral nutrition were similar for both groups on days 0 through 12 (eTable), and the P value for interaction with the EDEN study was .47. Patients in both groups received an average of 85% of the planned twice-daily dosages of the study supplement. Patients receiving the n-3 supplement had more frequent instances of gastrointestinal intolerance. Diarrhea occurred in 28.7% and 20.9% of ventilated days in the n-3 and control groups, respectively (P = .001). Both groups experienced similar incidences of gastric residual volumes greater than 400 mL (3.2% vs 4.0%; P = .30), abdominal distention (9.3% vs 7.4%; P = .19), and vomiting (3.8% vs 2.4%; P = .09).

Baseline plasma levels of EPA were about 2 mg/L in both groups (Figure 2). The n-3 study supplement increased plasma EPA levels 8-fold on days 3, 6, and 12, whereas levels in control patients remained unchanged (Figure 2). Plasma levels of the n-6 arachidonic acid did not change in either group over the first 12 study days. The resulting change in plasma fatty acid levels (eFigure 1) did not alter plasma levels of IL-6 or IL-8, which decreased similarly in both groups on days 3 and 6 (eFigure 2A). Likewise, plasma leukotriene E₄ levels did not change on study day 6 in either group (eFigure 2B). The n-3–derived leukotriene E₅ was undetectable in plasma in both groups at baseline and on day 6. Urinary levels of F₂-isoprostane, the lipid peroxidation stress marker derived from n-6 fatty acids, were similar in both groups at baseline and did not change significantly in either group on day 6. Urinary levels of F₂-isoprostanes, derived from n-3 fatty acids, were also similar at baseline but were significantly higher in the n-3 group on day 6 compared with controls (eFigure 2C).

Table 2. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n-3 (n = 143)</th>
<th>Control (n = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>55.5 (17.0)</td>
<td>52.9 (16.5)</td>
</tr>
<tr>
<td>Women</td>
<td>68 (48)</td>
<td>65 (50)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White (not Hispanic)</td>
<td>102 (71)</td>
<td>94 (73)</td>
</tr>
<tr>
<td>Black (not Hispanic)</td>
<td>27 (19)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (5)</td>
<td>16 (12)</td>
</tr>
<tr>
<td>Other/NA</td>
<td>5 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>46 (32)</td>
<td>42 (33)</td>
</tr>
<tr>
<td>Medical ICU</td>
<td>122 (85)</td>
<td>111 (86)</td>
</tr>
<tr>
<td>APACHE III score, mean (SD)</td>
<td>93.8 (24.9)</td>
<td>91.8 (29.3)</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>78 (55)</td>
<td>62 (48)</td>
</tr>
<tr>
<td>Propofol use</td>
<td>43 (30)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>Baseline propofol infusion rate, median (IQR), mg/h</td>
<td>30.0 (11.0-80.0)</td>
<td>26.5 (8.0-107.0)</td>
</tr>
<tr>
<td>Nonpulmonary organ or system failures (maximum of 4), mean (SD), No.</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.9)</td>
</tr>
<tr>
<td>Arterial pressure, mean (SD), mm Hg</td>
<td>75.1 (13.2)</td>
<td>76.7 (15.3)</td>
</tr>
<tr>
<td>Central venous pressure, mean (SD), mm Hg</td>
<td>10.7 (4.9)</td>
<td>11.2 (4.1)</td>
</tr>
<tr>
<td>Prestudy fluid intake, mean (SD), mL/24 h</td>
<td>5085 (3543)</td>
<td>4387 (3063)</td>
</tr>
<tr>
<td>Albumin, mean (SD), g/dL</td>
<td>2.3 (0.7)</td>
<td>2.2 (0.7)</td>
</tr>
<tr>
<td>Tidal volume, mean (SD), mL/kg</td>
<td>7.0 (1.6)</td>
<td>6.8 (1.3)</td>
</tr>
<tr>
<td>Plateau airway pressure, mean (SD), cm H₂O</td>
<td>23.3 (4.8)</td>
<td>22.8 (5.5)</td>
</tr>
<tr>
<td>PEEP, mean (SD), cm H₂O</td>
<td>8.6 (3.5)</td>
<td>8.7 (3.3)</td>
</tr>
<tr>
<td>Minute ventilation, mean (SD), L/min</td>
<td>11.4 (3.1)</td>
<td>10.6 (2.9)</td>
</tr>
<tr>
<td>Respiratory rate, mean (SD), breaths/min</td>
<td>25.7 (7.2)</td>
<td>24.7 (7.2)</td>
</tr>
<tr>
<td>Pao₂/Fio₂ ratio, mean (SD)</td>
<td>159.9 (75.6)</td>
<td>172.5 (84.6)</td>
</tr>
<tr>
<td>Oxygenation index, mean (SD)</td>
<td>11.7 (7.4)</td>
<td>10.5 (7.3)</td>
</tr>
</tbody>
</table>

Abbreviations: APACHE III, Acute Physiology and Chronic Health Evaluation III; Fio₂, fraction of inspired oxygen; ICU, intensive care unit; IQR, interquartile range; NA, not available; n-3, omega-3; Pao₂, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

Higher scores indicate a higher severity of illness.

The n-3 group had a higher minute ventilation and trend toward greater net fluid administration in the 24-hour preenrollment period than the control group.
The omega-3 (n-3) supplement comprised the n-3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, the omega-6 γ-linolenic acid, and antioxidants. Error bars indicate 95% confidence intervals. Positive end-expiratory pressure (PEEP) was similar between groups during the study; plateau pressures were similar between groups except day 2 during the first week ($P=.04$). Oxygenation (ratio of partial pressure of arterial oxygen [$PaO_2$] to fraction of inspired oxygen [$FIO_2$]) did not differ between groups.

**Baseline Characteristics and Study Variables**

Baseline characteristics are shown in **Table 2**. Pneumonia (52%) and sepsis (23%) were the most common etiologies of ALI. Although both groups had similar APACHE III scores, the n-3 group had higher minute ventilation (11.4 [SD, 3.1] L/min vs 10.6 [SD, 2.9] L/min; $P=.04$). Baseline creatinine, glucose, and albumin levels were similar between groups.

Over the first 7 days, both groups had similar values for heart rate, systolic blood pressure, respiratory rate, and temperature. Values also were similar for positive end-expiratory pressure, plateau pressure, and PaO$_2$:FIO$_2$ ratio (**Figure 3**) and minute ventilation and partial pressure of arterial carbon dioxide (**Figure 4**).

Serum albumin and protein levels did not differ between groups at baseline or during the study. Baseline serum glucose values were similar in both groups (134 [SD, 55] mg/dL vs 125 [SD, 47] mg/dL; $P=.17$) and consistently averaged less than 150 mg/dL in both groups through day 7 (**eFigure 3**). Patients in both groups received an average of slightly more than 1 unit of insulin per hour over the first 7 days (**eFigure 3**).

Numerically more patients in the n-3 group were receiving vasopressors at enrollment, a difference that persisted through day 7 (**eFigure 4**). The n-3 group had a trend toward more net fluid administration in the 24 hours prior to enrollment (5085 [SD, 3543] mL vs 4387 [SD, 3063] mL; $P=.09$). The n-3 group also had a trend toward greater cumulative fluid balance over the first 7 study days (2082 [SD, 8088] mL vs 94 [SD, 7071] mL; $P=.07$). No differences in the development of new infections were found between groups (ventilator-associated pneumonia, 7% [95% CI, 3%-11%] for the n-3 group vs 8% [95% CI, 3%-12%] for the control group [$P=.81$]; bacteremia, 11.2% [95% CI, 6%-16.4%] vs 10.9% [95% CI, 5.5%-16.2%] [$P=.91$]; or *Clostridium difficile*-associated diarrhea, 4.2% [95% CI, 1.6%-8.9%] vs 3.9% [95% CI, 1.3%-8.8%] [$P=.98$]).

**Clinical Outcomes**

The n-3 supplement group had fewer VFDs to study day 28 compared with controls (14.0 [SD, 11.1] vs 17.2 [SD, 10.2], $P=.02$) (difference, −3.2 [95% CI, −5.8 to −0.7]) and fewer ICU-free days (14.0 [SD, 10.5] vs 16.7 [SD, 9.5], $P=.04$ (**Table 3**). In the n-3 group, 38
DIETARY SUPPLEMENTATION IN ACUTE LUNG INJURY

Table 3. Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n-3 (n = 143)</th>
<th>Control (n = 129)</th>
<th>Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-free days from day 1 to day 28</td>
<td>14.0 (11.1)</td>
<td>17.2 (10.2)</td>
<td>−3.2 (−5.8 to −0.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Death before discharge home, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>26.6 (19.3-33.8)</td>
<td>16.3 (9.9-22.7)</td>
<td>10.3 (0.7 to 19.9)</td>
<td>.054</td>
</tr>
<tr>
<td>Adjusted for differences in baseline covariates</td>
<td>25.1 (9.2-41.0)</td>
<td>17.6 (3.3-31.9)</td>
<td>7.5 (−3.1 to 18.1)</td>
<td>.11</td>
</tr>
<tr>
<td>No. of days not spent in an intensive care unit from day 1 to day 28</td>
<td>14.0 (10.5)</td>
<td>16.7 (9.5)</td>
<td>−2.7 (−5.1 to −0.3)</td>
<td>.04</td>
</tr>
<tr>
<td>No. of days without failure of circulatory, coagulation, hepatic, or renal organs from day 1 to day 28</td>
<td>12.3 (11.1)</td>
<td>15.5 (11.4)</td>
<td>−3.2 (−5.9 to −0.5)</td>
<td>.02</td>
</tr>
</tbody>
</table>

25.1% (95% CI, 9.2%-41.0%) 60-day mortality vs 17.6% (95% CI, 3.3%-31.9%) in the control group (P = .11).

Probabilities of survival and breathing without assistance to day 60 for both groups are shown in Figure 5.

COMMENT

In contrast to previous studies,12-14 in this study enteral supplementation of n-3 fatty acids, GLA, and antioxidants did not improve lung physiology or clinical outcomes in patients with ALI compared with supplementation of an isocaloric control. In addition, the n-3 supplement did not protect from nosocomial infections or improve nonpulmonary organ function.

Several noteworthy differences between the current and previous studies may explain the observed differences. The 3 previous studies used continuous enteral infusions to deliver the supplements, whereas we used bolus delivery. Previous studies required patients to tolerate a specific goal feeding rate, either to enter the trial or to be included in the analysis, and many randomized patients were unable to tolerate the required infusion rates, introducing potential bias. To increase the likelihood that the treatment would be tolerated, our study used a small-volume supplement (120 mL) twice daily to deliver similar doses of n-3 fatty acids, GLA, and antioxidants, as were given in previous studies. We used an intention-to-treat analysis, which accounted for all randomized patients. It is possible that bolus administration of the high-fat supplement may have caused the increased incidence of diarrhea observed in the n-3 group.

Another major difference between this and previous studies is the composition of the control supplement. The control in the previous studies12-14 was a commercially available, high-fat formulation containing predominately n-6 and omega-9 (n-9) fatty acids selected to match the percentage of calories from fat, protein, and carbohydrate in the n-3 formulation. In contrast, our study used an isocaloric supplement containing mostly carbohydrate calories instead of lipids. Because n-6 and n-9 fatty acids can be metabolized into inflammatory prostaglandins and series-4 leukotrienes,76 it is possible that the control formulations in previous studies may have been proinflammatory, accounting for the differences in outcomes between groups. However, we found no improvement in clinical outcomes for n-3 fatty acid supplementation compared with a largely carbohydrate control.

We hypothesized that the n-3 supplement would improve clinical outcomes compared with the control supplement. We did not design our study to determine if the control supplement would yield better outcomes than the n-3 supplement. Thus, the efficacy and futility stopping boundaries were not symmetric, with stopping for futility being easier than for efficacy. The DSMB recommended terminating the study at the first interim analysis because the primary end point (VFDs) and the major secondary end point (mor-
tality) crossed the predefined futility boundaries, making the probability of a positive trial going forward very low. Despite P values of .02 and .054 for VFD and mortality, respectively, we cannot confidently conclude there was harm in the n-3 group, because this may have been a chance observation.21 For example, if our stopping boundaries for efficacy and futility had been the same, P < .001 would have been required at the first interim analysis to conclude that the control supplement was superior. In addition, there was slight imbalance of age, APACHE III score, PaO₂/FIO₂ ratio, and minute ventilation favoring the control group.

Nonetheless, it remains possible that there is a hierarchy of energy sources in patients with ALI. Carbohydrates and protein (as in our control) may result in better clinical outcomes than lipids, and at the same time n-3 fatty acids may result in better clinical outcomes than n-6 and n-9 fatty acids. Historically, carbohydrates have been avoided in ventilated patients because of concerns regarding hyperglycemia and increased production of carbon dioxide.22 The extra carbohydrates in the control supplement of our study did not appear to exacerbate either hyperglycemia or hypercapnea. However, our study attempted to maintain blood glucose levels less than 150 mg/dL,23 and overall mean serum glucose and insulin utilization were similar in the 2 groups.

Last, we controlled mechanical ventilation and fluids, nonexperimental covariates that have been shown to affect clinical outcomes in ALI.6,17 Interpretation of results of the previous trials may be limited by the diversity of these important therapeutic interventions. Beyond reducing mortality and ventilator time, lung-protective ventilation has also been shown to decrease systemic inflammation and organ dysfunction.24 It is possible that the anti-inflammatory effects of lung-protective ventilation obscured further reductions associated with use of the n-3 supplement. Similarly, the use of a conservative fluid-management strategy has been shown to expedite liberation from the ventilator,17 further reducing opportunity for new interventions to show benefit. Despite enrolling a population with high severity of illness, overall mortality in this study was only 21.7%, considerably lower than that seen in the 3 previous studies of n-3 fatty acids12-14 and in other studies of patients with ALI.6,17,20

Despite significant increases in plasma n-3 levels, we did not demonstrate a reduction in levels of inflammatory biomarkers. The reason why twice-daily supplementation failed to alter plasma biological marker levels is unclear. It is possible that more frequent or near-continuous dosing is necessary to see benefits. Although incorporation of n-3 fatty acids into cell membranes was not directly measured, data suggest that plasma levels correlate well with phospholipid membrane content,25,26 suggesting that our administration of n-3 fatty acids should have had a biological effect. Although the EPA and DHA dosages administered in this study were similar to those used in previous studies12-14 we did not measure actual pharmacokinetics, so we cannot directly compare with the serum EPA levels reported by Gadek et al.12

Reduced levels of IL-8 and leukotriene B4 in bronchoalveolar lavage fluid have been observed in patients with ALI treated with n-3 fatty acids and correlated with improvements in pulmonary physiology.27 Although we did not perform bronchoalveolar lavage, we did not find any improvement in respiratory physiology, specifically PaO₂/FIO₂ ratio, positive end-expiratory pressure, and plateau pressure in patients receiving the n-3 supplement. It is possible the relatively short duration of acute illnesses like ALI, coupled with current treatment modalities with lung-protective ventilation and conserva- tive fluid management, may not allow enough time for enteral n-3 fatty acid supplementation to have effect. However, fatty acid composition and cell responses to stimuli may be modified within hours of treatment with EPA or DHA, and modest doses alter plasma and cellular content within 1 to 3 days.28 Even parenteral administration of n-3 fatty acids, which would presumably alter plasma and cellular content more quickly, has failed to alter the inflammatory response in critically ill patients.29,30

CONCLUSIONS

This study suggests that twice-daily enteral supplementation of n-3 fatty acids, GLA, and antioxidants change plasma levels of n-3 fatty acids but do not improve clinical outcomes or biomarkers of systemic inflammation in patients with ALI and in fact may be harmful.

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Author Contributions: Dr Thompson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: Rice, Wheeler, Thompson, Steingrub, Rock.

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REFERENCES


Online-Only Material: The eMethods, eTable, and eFigures 1–4 are available at http://www.jama.com.

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