Fish Oil in Sepsis: If You Want to Catch More Fish, Use More Hooks

Dear Editor,

We read with interest the article by Wohlmuth et al[1] attempting to detect outcome effects of intravenous (IV) fish oil (FO) supplementation in patients with sepsis from an abdominal source. The retrospective screening of the authors' database revealed 194 abdominal sepsis patients, of whom 42 received a 10-g intravenous FO bolus (over 30-60 minutes) per day. FO administration was started on the first postoperative day or upon intensive care unit (ICU) admission for a maximum of 7 days or until ICU discharge.

Twenty-nine of the 42 FO-treated patients were matched with 29 historical septic control patients for comparison. The propensity score adjustment for confounding factors within was derived from a logistic regression model. Factor selection for the regression model by the authors was done with regard to either statistical or biological outcome relevance. The factors included were age, gender, body mass index (BMI), admission diagnosis, Simplified Acute Physiology Score II (SAPS II), presence of chronic obstructive pulmonary disease, heart disease, chronic renal insufficiency, cirrhosis, hypertension, carcinoma, and need for mechanical ventilation. The authors correctly concede the substantial risk of unequal risk distribution over the groups within their retrospective observation. With such a small sample, the adequacy of the models used to inform the propensity analysis is suspect (standard β, R^2 not reported). Furthermore, biologically relevant factors were not considered such as white blood cell count, C-reactive protein or other markers of systemic inflammation, timing of onset of sepsis, individual caloric demand, accomplished caloric delivery, or the need for continuous renal replacement therapy. The lack of analysis of 13 of the 42 FO patients (31%) also exposes the study to selection bias.

In studies concerning septic shock, timing of treatment is of exceptional relevance,[2,3] and immunologic FO effects after single administration fade away within 24 hours.[4] In the present study, FO administration was not harmonized with the onset of sepsis.

Moreover, the most striking flaw of the retrospective analysis is the missing weight adjustment of the FO dose and subsequent underdosing and at the same time fat overload because of too rapid infusion. Body weight of the study population was not given. Assuming that a BMI of 25 kg/m^2 (interquartile range [IQR] 22-29) in Austrian people will originate from a weight of 80 kg (IQR 70-90), the median dose must have been around 0.12 g/kg/d FO (IQR 0.11-0.15). All positive prior studies including FO used considerably higher doses (for review, see Chen et al[5]). Present dosages are fairly comparable to one group receiving 0.1-0.15 g/kg/d from an earlier study,[6] but lower antibiotic demand was reported when doses of at least 0.15-0.2 g/kg/d were infused. Furthermore, regression analysis showed an optimum dose of 0.23 g/kg/d in septic patients with a short ICU stay.[6] So the underdosing of FO in the present work independently makes outcome effects unlikely. But more importantly, the authors infused 10 g FO over 30-60 minutes, which by far exceeds the approved limit of 0.05 g/kg/h for infusion speed of the used lipid emulsion. An 80-kg patient then would have received up to 0.25 g/kg/h (30-minute infusion). Considering the reported IQR of BMI, 25% of patients had a body weight of 70 kg or lower. They even received up to 0.29 g/kg/h (30-minute infusion). Lekka et al[7] and Suchner et al[8] independently found that lipid infusion with 0.21 or 0.22 g/kg/h aggravated lung injury with respect to shunt fraction, oxygenation index, pulmonary vascular resistance, and compliance when infused over 1 or 6 hours, respectively. So both inadequate low dosing and fast timing of the n-3 lipids in the present study were at least inefficient and may have even caused harm in these septic patients. No wonder the authors were not able to demonstrate any treatment effect.

Notwithstanding the methodological deficiencies previously outlined, the present study lacked sufficient power to comment on a clinically important treatment effect. Chen et al[5] calculated a slightly significant (P = .04) risk reduction for postoperative infection after FO to 0.56 (95% confidence interval [CI], 0.32-0.98). The underlying case load was n = 529 from 7 randomized controlled trials. So the present analysis of 2 × 29 patients

is clearly underpowered for the selected primary endpoint (new onset of organ failures) and, consequently, is prone to a type II error ("absence of evidence is not evidence of absence").

In summary, the observation by Wohlmuth et al[1] is flawed by several substantial pharmacological and statistical problems (underdosing of FO, fat overload, selection bias, inadequate sample size, unclear timing, and questionable propensity adjustment), invalidating any clinical conclusions on the effects of FO on clinical outcomes in abdominal sepsis.

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