Letter to the Editor

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Dear Editor,

In their meta-analysis of randomized controlled trials published in the July 2010 issue of the *Journal of Parenteral and Enteral Nutrition*, Chen et al[1] provided readers with science-based conclusions concerning the safety and efficacy of using fish oil–enriched parenteral nutrition(PN) to decrease the postoperative infection rate and length of stay in hospitals and intensive care units (ICUs) of patients undergoing major abdominal surgery.

A previous meta-analysis of parenteral infusion of fish oil lipid emulsion (LE) failed to confirm any potential benefits.[2] Despite the scientific rigor applied to gathering, selecting, and examining the scientific data, the conclusions from the previous meta-analysis were susceptible to limitations, including the evaluation of a heterogeneous population, because both surgical and critically ill patients were considered.[2] We believe that by choosing a more homogeneous population, Chen et al obtained more consistent conclusions. In fact, these authors confirmed the reduced infectious complication rate and length of hospital stay reported by other current meta-analyses enrolling a small number of European and Asian studies with surgical patients treated with fish oil–enriched PN.[3]

Major abdominal surgery can lead to an excessive systemic inflammatory response, which in turn increases the risk of postoperative complications and multiple organ failure.[4] Several reports have indicated that ω-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from fish oil, can prevent the development of inflammatory diseases, because these PUFAs directly or indirectly affect different steps of the immune response. In addition, they possess biological properties that can mitigate preexisting inflammatory processes, contributing to their beneficial effects.[5] Thus, fish oil–enriched parenteral regimens have potential benefits for patients undergoing abdominal surgery.

The conclusions of the Chen et al[1] meta-analysis are in line with the overall impressions of our team, which are based on several clinical trials that found a positive association between fish oil–enriched PN and maintenance and improvement of immune variables and clinical outcomes. However, it is worth noting that Chen et al selected trials that compared the effect of parenteral regimens enriched with fish oil LE with parenteral regimens containing soybean LE, which is rich in ω-6 PUFAs and thus potentially immunosuppressive.[6-18] Thus, it is difficult to conclude definitively whether the benefits that Chen et al observed in their meta-analysis arose from the higher amount of ω-3 PUFAs provided by fish oil–containing LEs or whether they instead reflect a comparatively lower level of immune impairment induced by the high amounts of ω-6 PUFAs delivered by soybean oil LE.

To better support the final conclusions of the Chen et al[1] meta-analysis, further studies are required to evaluate the benefits of fish oil–enriched parenteral regimens compared with emulsions less likely than soybean oil LE to be immunosuppressive, for example, LE rich in medium-chain triglycerides and olive oil–based LE.[19] Issues regarding clinical trial design for studies of fish oil LE should be considered and warrant further discussion.

Parenteral infusion of fish oil leads to the rapid incorporation of ω-3 PUFAs by leukocytes; furthermore, this route avoids the loss of fatty acids that occurs during digestion and absorption following oral and enteral intake. Reduced monocyte proinflammatory cytokine generation and adhesive interactions with endothelium were observed 48 hours after infusion in healthy volunteers, suggesting that parenteral delivery of ω-3 PUFAs could contribute to its early immune-modulating effects.[20] Most surgical patients do not require PN; therefore, we believe that future studies of fish oil–containing parenteral regimens in patients who are undergoing surgery should investigate the use of fish oil not only as part of a PN regimen, but also as a pharmacological agent to rapidly modulate immunological markers and possibly improve clinical outcomes.

Fish oil–containing LEs for clinical use are composed of pure fish oil or mixtures of fish oil with other oils (soybean oil, medium-chain triglycerides from coconut oil, and olive oil). Although the infusion of LEs containing fish oil in mixtures with other oils is safe, LEs composed of pure fish oil have been infused as a supplement to other standard LEs.[19] However, as recently demonstrated in a pilot study by Bahadori et al,[21] the infusion of pure fish oil LE at 0.2 kg of fat per body weight was safe and well tolerated and also efficient in improving clinical

symptoms of patients with rheumatoid arthritis.[21] These findings point out the safety of using pure fish oil LE as a pharmacological agent.

The precise point at which fish oil–containing LEs are infused may be crucial and should be considered. There is a growing body of evidence that a preoperative supply of nutrients that modulate immune functions, including ω-3 PUFAs, is more effective than a postoperative supply with regard to clinical benefits.[22] A retrospective study by Tsekos et al[23] found lower mortality rates, less need for mechanical ventilation, and reduced infection rates and hospital stays in a group treated preoperatively with PN containing fish oil vs standard PN. When infused only in the postoperative period, fish oil–enriched PN did not affect hospital stay and mortality rates.[23]

Finally, fish oil–containing LEs may have increased benefits for surgical patients with additional risk factors for infections, such as advanced age and malnutrition.[24] For example, Heller et al[25] did not find any changes in the clinical outcome of a group of surgical patients treated with fish oil LE; however, the investigators observed a shorter length of ICU stay when only those surgical patients at risk for sepsis were analyzed.[25] Therefore, studies evaluating the effect of fish oil–containing LEs in surgical patients should evaluate higher risk groups separately. This may be useful for identifying those surgical patients who might benefit most from parenteral infusion of fish oil.

In summary, clinical trials evaluating the effect of fish oil–containing LEs should include more appropriate controls, use randomized and double-blind designs, and consider the issues emerging from cumulative evidence in this area of investigation. The impact of potential immune modulation on patient outcome (mortality, length of hospital and ICU stay, and infection rates), and cost-effectiveness should be investigated to determine whether there is a potential clinical value in using fish oil–containing LEs to treat surgical patients.

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