



# Clinical impact of omega-3 fatty acids ( $\Omega$ 3 FA) supplementation on liver surgery

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*Comment on:* Linecker M, Botea F, Aristotele Raptis D, *et al.* Perioperative omega-3 fatty acids fail to confer protection in liver surgery: Results of a multicentric, double-blind, randomized controlled trial. *J Hepatol* 2020;72:498-505.

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Omega-3 fatty acids ( $\Omega$ 3 FA) are essential nutritional components with beneficial effects on fatty liver and metabolic syndrome affecting blood lipid profiles, membrane lipid composition, eicosanoid biosynthesis, cell signaling cascades, and gene expression (1). They are also involved in a number of metabolic process, including inhibition of several aspects of inflammation, such as leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes, production of inflammatory cytokines and T cell reactivity (2).  $\Omega$ 3 FA are particularly abundant in fish and other seafood.

$\Omega$ 3 FA supplementation have been proposed for the prevention of several diseases including different forms of cancer, coronary artery disease, cerebrovascular disease, developmental disabilities, depression, bipolar illness, cognitive decline, Alzheimer disease, macular degeneration, rheumatoid arthritis, eczema and allergic conditions (3). In the setting of liver diseases,  $\Omega$ 3 FA have been shown to have a beneficial effect on non-alcoholic fatty liver disease (4), allowing diminution of intrahepatic lipid contents and mitigation of inflammation (2). Supplementation of  $\Omega$ 3 FA was related to a significant benefit for liver steatosis, insulin resistance, and level of alanine aminotransferase, aspartate aminotransferase,  $\gamma$ -glutamyl transferase, triglycerides, insulin resistance, and glucose (5).

Four-week supplementation before bariatric surgery has shown to reduce liver volume and facilitate bariatric procedure in obese patients (6). In liver surgery, experimental models have demonstrated that  $\Omega$ 3 FA allows

reduction of liver fibrosis, improvement of cirrhotic liver regeneration (7), and protection from ischemia/reperfusion injury (8). According to these premises, a benefit of supplementation of  $\Omega$ 3 FA has been hypothesized for patients undergoing liver surgery.

In this setting, the recent randomized trial by Linecker *et al.* (9) published in the October, 2019 issue of *Journal of Hepatology* provides major information on the impact of perioperative  $\Omega$ 3 FA in patients undergoing liver surgery. The study is a multicentric, double-blind trial and has a robust methodology, which confers high relevance to the obtained results. A total of 261 patients have been included and randomized to the administration of (I) two doses of 10 g highly refined fish oil containing eicosapentaenoic and docosahexaenoic acid or (II) placebo. Inclusion criteria are strict, and only adult patients without coagulopathy (as assessed by INR and platelet count) undergoing at least resection of 1 liver segment or 3 wedge resections were selected. Cirrhotic patients and pregnant women were excluded. Results are very detailed, including complete analysis of the laboratory parameters and postoperative outcomes in the first 30 days. This study shows that preoperative intravenous infusion of  $\Omega$ 3 FA does not reduce morbidity and mortality after liver surgery. Even secondary analysis including only patients undergoing major liver resections and only those who received Pringle maneuver fails to demonstrate some advantages in morbidity or mortality related to the administration of  $\Omega$ 3 FA. Bioavailability of  $\Omega$ 3 FA is confirmed by the modifications of blood levels of triglycerides, increased in the Omegavan<sup>®</sup>

**Table 1** Randomized clinical trials analyzing the impact of omega-3 supplementation in the setting of liver surgery

Author, year	N.	Procedure	Protocol	Significant results
Linecker, 2020	261	Liver resection	Omegavan 10% 100 mL per day the evening before surgery and the day of surgery	0
Zhang, 2017	312	Liver resection for cancer in cirrhotic patients	Intravenous Omegavan® 10% 100 mL during 5 consecutive postoperative days	Reduction of morbidity, mortality, and length of stay
Ibrahim, 2016	40	Living donor liver transplantation	Intravenous Ω3 FA enriched lipid emulsion 20% by (7 mL/kg) (soya oil, medium chain triglycerides, olive oil, fish oil lipid 20%, Fresenius Kabi) at 0.63 mL/(kg·h) once a day during 2 days before partial hepatectomy and postoperatively at day 0	Increase of liver volume after 1 months, higher regeneration index and percentage
Gong, 2016	119	Liver resection for liver cancer, liver metastases or intrahepatic lithiasis	Intravenous Omegavan® 10% 100 mL/day started 12 to 24 hours after surgery during 5 days	Lower rate of total complications and infections
Zhu, 2012	66	Orthotopic liver transplantation for end-stage liver disease or hepato cellular carcinoma	Omegavan 10%, 2 mL/kg per day, Fresenius Kabi during seven days from the second postoperative day	Decrease of length of stay

group, whereas no significant change was found in levels of platelet, INR, transaminases. Of note, three patients without previous cardiac diseases in the Omegavan® group died for cardiac events (arrhythmia, ischemia, unclear). In contrast, the placebo group revealed no lethal cardiac event (the difference was not statistically significant). Even if this finding does not allow any relevant conclusion about the risk of cardiac event in patients receiving Ω3 FA supplementation in this setting, it represents a possible concern. The authors conclude that administration of two doses of Ω3 FA in patients undergoing hepatectomy is not useful.

Several previous randomized trials analyzing the role of Ω3 FA supplementation gave different results, and advocated a positive effect of Ω3 FA administration on postoperative outcomes (Table 1). Zhu *et al.* (10) administered Omegavan® 10% during 7 postoperative days after liver transplantation, showing in the Ω3 group lower score of portal inflammation, decreased level of ALT and PT at day 9, and a reduced length of hospital stay. Gong *et al.* (11), in a population of patients undergoing minor and major hepatectomies, found that Omegavan® administered during 5 days starting 12 to 24 hours after surgery was able to significantly reduce the total complication rate (25.4% in the control group versus 41.7% in the treatment group) and the length of hospital stay. At postoperative day 3 and 7, a significant reduction of leucocytes, transaminases and bilirubin was observed in the Ω3 FA group. The decrease

of prothrombin time was significantly lower in the Ω3 group. Ibrahim and colleagues (12) studied the effect of Ω3 FA on liver donors. Their protocol consisted in the administration of an enriched Ω3 FA emulsion the day before surgery and the day of surgery. The authors found lower values of transaminases, white blood cells and C reactive protein in the omega-3 group at postoperative day 1, 3, 5, 7, and higher level of hepatocyte growth factor at postoperative day 1, 3, 5. Regeneration index and liver volume at 1 month were significantly higher in patients receiving Ω3 FA supplementation. No major complication was observed in both groups and no transfusion was needed. Zhang *et al.* (13) administered Omegavan® 10% 100 mL during 5 days postoperatively to cirrhotic patients who underwent hepatectomy for cancer. They demonstrated a significant reduction of overall complications (50.32% in the control group versus 29.30% in the treatment group), infectious complications (19.35% in the control group versus 9.55% in the treatment group), intra-abdominal infections (7.74% versus 1.91%), In the treatment group, a reduction of ALT and C reactive protein was found at day 3 and 5. As shown in Table 1, these previous studies suggested a positive effect of omega-3 supplementation on clinical outcomes, whereas the recent randomized trial by Linecker *et al.* did not.

How can we explain these different findings? Has the administration of Ω3 FA a clinical impact in patients candidates to liver surgery?

The mentioned studies, even if they are all randomized

trials, are heterogeneous in patients' inclusion, type of liver surgery, protocols of  $\Omega 3$  FA administration and outcomes. Only Linecker *et al.* (9) and Ibrahim *et al.* (12) choose a protocol of 2-day administration of  $\Omega 3$  FA, (one day before surgery and the day of surgery). However, the latter study included living liver donors and performed an analysis of liver volume and regeneration, whereas the first focused on postoperative complications.

An important consideration is that  $\Omega 3$  FA have two potential main effects in the setting of liver surgery: (I) an antioxidative/anti-inflammatory effect, and (II) an impact on liver defatting and regulation of hepatocytes metabolism (14). In the study by Linecker *et al.* (9), only the antioxidative/anti-inflammatory effect may be detected, because the patients were not followed beyond 30 days and the liver volume and function in the late postoperative period were not analyzed. On the other hand, Ibrahim *et al.* demonstrated the impact of such a short-period administration of  $\Omega 3$  FA on liver regeneration, with liver volumetry and analysis of regeneration index at 30 days. Both studies failed to demonstrate a clinical impact on morbidity and mortality of a 2-day  $\Omega 3$  FA supplementation.

The remaining 3 studies (10,11,13) were based on a longer period of  $\Omega 3$  FA administration, ranging from 5 to 7 days. These studies were also heterogeneous: Zhang *et al.* focused on cirrhotic patients (13), Zhu *et al.* included patients undergoing liver transplantation (10). These studies demonstrated a clinical impact of  $\Omega 3$  FA supplementation on short-term clinical outcomes, showing a reduction of postoperative morbi-mortality rate (11,13), infectious complications (11), and length of hospital stay (10,13). Even if these data are difficult to interpret, because of the differences of patients characteristics, we can hypothesize that a longer period of administration of  $\Omega 3$  FA emulsions may have a stronger clinical effect in the setting of liver surgery.

In conclusion, the study of Linecker *et al.* has a high methodological quality, and questions the clinical utility of  $\Omega 3$  FA supplementation. Their 2-day protocol did not have any impact on postoperative morbi-mortality. It would be interesting to assess a third arm of patients receiving supplementation during a longer period (5–7 days), like in the studies showing a positive clinical effect.

So, several questions are opened by the study by Linecker *et al.*: (I) has the  $\Omega 3$  FA supplementation a clinical effect? (II) what is the most effective protocol of  $\Omega 3$  FA administration in the setting of liver surgery? (III) what kind of patients may benefit from 3 FA supplementation?

Future trials are needed to clarify these interesting topics, and may have a potential impact on routine clinical practice in the setting of liver surgery.

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