Liver-protecting effects of omega-3 fish oil lipid emulsion in liver transplantation

Xin-Hua Zhu, Ya-Fu Wu, Yu-Dong Qiu, Chun-Ping Jiang, Yi-Tao Ding

Xin-Hua Zhu, Ya-Fu Wu, Yu-Dong Qiu, Chun-Ping Jiang, Yi-Tao Ding, Department of Hepatobiliary Surgery, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing 210008, Jiangsu Province, China

Author contributions: Zhu XH performed the literature review and part of the surgery, and prepared the manuscript; Wu YF performed part of the surgery and offered help with manuscript preparation and literature review; Qiu YD performed part of the surgery, the collection of clinical data and the statistical analysis; Jiang CP helped collect clinical data and performed part of the surgery; Ding YT instructed the manuscript preparation and performed part of the surgery.

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Correspondence to: Yi-Tao Ding, MD, Professor, Department of Hepatobiliary Surgery, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Zhongshang Road 321, Nanjing 210008, Jiangsu Province, China. drzhuxh@163.com

Telephone: +86-25-83304616 Fax: +86-25-83317016

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Abstract

AIM: To investigate the liver-protecting effect of parenteral nutrition (PN) support with omega-3 fatty acids in a randomized controlled clinical trial.

METHODS: Sixty-six patients with the diagnosis of end-stage liver disease or hepatic cellular carcinoma were admitted to the Affiliated Drum Tower Hospital, Nanjing University, China for orthotopic liver transplantation. The patients were randomly divided into two groups: PN group (n = 33) and polyunsaturated fatty acid (PUFA) group (n = 33). All patients received isocaloric and isonitrogenous PN for seven days after surgery, and in PUFA group omega-3 fish oil lipid emulsion replaced part of the standard lipid emulsion. Liver function was tested on days 2 and 9 after surgery. Pathological examination was performed after reperfusion of the donor liver and on day 9. Clinical outcome was assessed based on the post-transplant investigations, including: (1) post-transplant mechanical ventilation; (2) total hospital stay; (3) infectious morbidities; (4) acute and chronic rejection; and (5) mortality (intensive care unit mortality, hospital mortality, 28-d mortality, and survival at a one-year post-transplant surveillance period).

RESULTS: On days 2 and 9 after operation, a significant decrease of alanine aminotransferase (299.16 U/L ± 189.17 U/L vs 246.16 U/L ± 175.21 U/L, P = 0.024) and prothrombin time (5.64 s ± 2.06 s vs 2.54 s ± 1.15 s, P = 0.035) was seen in PUFA group compared with PN group. The pathological results showed that omega-3 fatty acid supplement improved the injury of hepatic cells. Compared with PN group, there was a significant decrease of post-transplant hospital stay in PUFA group (18.7 d ± 4.0 d vs 20.6 d ± 4.6 d, P = 0.041). Complications of infection occurred in 6 cases of PN group (2 cases of pneumonia, 3 cases of intra-abdominal abscess and 1 case of urinary tract infection), and in 3 cases of PUFA group (2 cases of pneumonia and 1 case of intra-abdominal abscess). No acute or chronic rejection and hospital mortality were found in both groups. The one-year mortality in PN group was 9.1% (3/33), one died of pulmonary infection, one died of severe intra-hepatic cholangitis and hepatic dysfunction and the other died of hepatic cell carcinoma recurrence. Only one patient in PUFA group (1/33, 3.1%) died of biliary complication and hepatic dysfunction during follow-up.

CONCLUSION: Post-transplant parenteral nutritional support combined with omega-3 fatty acids can significantly improve the liver injury, reduce the infectious morbidities, and shorten the post-transplant hospital stay.

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Key words: Fish oil lipid; Liver; Transplantation; Paren-
Liver transplantation has dramatically improved the prognosis of end-stage liver disease. The progress made in the immunosuppressive regimens and surgical techniques has yielded a better outcome of the patients, and the 5-year survival after liver transplantation is 70%-80%[2-3]. The liver recipients with liver insufficiency are in fact known to experience a higher incidence of severe protein/calorie malnutrition, which is associated with a greater risk of postoperative complications and mortality in patients undergoing liver transplantation[2,3]. And ischemia/reperfusion (I/R) injury associated with liver transplantation often leads to hepatic dysfunction despite the improvement in surgical techniques and perioperative medication. I/R injury of the liver is an event involving multiple factors, such as hypoxia during inflow occlusion of the liver and inflammatory reactions after reperfusion[4,5], and the mechanisms of the reperfusion injury, including the release of inflammatory cytokines, the generation of oxygen free radicals, Kupffer cell activation and leukocyte-endothelial cell interaction[6,7]. Based on the pathophysiology of hepatic I/R injury, the current study particularly focused on various perioperative approaches to protect the liver from these inflammatory reactions and microcirculatory disturbances.

Omega-3 (N-3) fatty acids, which are derived from fish oil, are essential polyunsaturated fatty acids (PUFAs) for humans. Omega-3 fatty acids exert anti-inflammatory and immunomodulatory properties through their ability to modulate the synthesis of different eicosanoids[8,9]. Perioperative administration of omega-3 fatty acids reduces plasma and tissue levels of the eicosanoids, specific leukotrienes, thromboxanes, and prostaglandins, all of which have pro-inflammatory effects[10,11]. Recent studies described that supplementation with omega-3 fatty acids decreases the rate of inflammatory complications, the length of hospital stay, and the mortality after major abdominal surgeries[12-14]. Their protective effects on hepatic I/R injury and inflammatory responses have been increasingly investigated.

In this study, we investigated the liver-protecting effects of parenteral nutrition (PN) supplemented with omega-3 fish oil lipid emulsion in patients undergoing liver transplantation.
the standard lipid emulsion (20% emulsion, with a ratio of long-chain triglycerides to medium-chain triglycerides of 1:1, Huarui Pharmaceuticals, Jiangsu, China) and in PUFA group omega-3 fish oil lipid emulsion (Omegaven, 10%, 2 mL/kg per day, Fresenius Kabi Co., Austria) replaced part of the standard lipid emulsion. Both groups received 1.0 g amino acid/kg per day, and they were administered a commercially available branched-chain amino acid solution ( Branched-chain amino acid solution 20%, Huarui Pharmaceuticals, Jiangsu, China). The ratio of nonprotein calories to nitrogen in both nutritional support groups was 653 kJ:1 g. The omega-3 fish oil lipid emulsion-containing solutions were prepared by the clinical pharmacist under aseptic condition and adjusted according to the weight of each individual patient. The amino acids, fat emulsion and dextrose mixture with electrolytes, vitamins, and trace elements were administered through a central venous catheter. As soon as the bowel function returned on days 3 or 4 after transplantation, all patients in the two groups were given liquid carbohydrate and cow’s milk protein.

The surgical treatment was standardized, and modified piggyback orthotopic liver transplantation was performed by three groups of surgeons using the same approach. After operation, all the patients in the two groups were treated with the same antibiotics and antivirutics, and 20 g of albumin was administered intravenously daily for five days to prevent any complications caused by hypoalbuminemia.

**Assessment**

Venous heparin blood samples were obtained on days 1 (the day before transplantation), 2 and 9 after surgery and liver function assessment was made. Serum total bilirubin (TB), direct bilirubin (DB), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and prothrombin time (PT) were measured by an automatic biochemical analyzer (HITA-CHI 7600, Japan).

Liver biopsy with fine needle was conducted after reperfusion of donor liver and on day 9 after surgery, respectively. Hepatic specimens for light microscopy were fixed with formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin for histological examination. Portal inflammation in the liver biopsy specimens was semiquantified by calculating inflammatory cells in portal tracts based on the Knodell histology activity index (HAI)

$\text{HAI} = \sum_{i=1}^{5} a_i$  

where $a_i$ is the activity score of the individual component of inflammation (HAI = 0-14). Portal inflammation was scored as 0, no portal inflammation; 1, mild (sprinkling of inflammatory cells in < 1/3 of portal tracts); 2, moderate (increased inflammatory cells in 1/3-2/3 of portal tracts); 3, moderate (increased inflammatory cells in > 2/3 of portal tracts).

The assessment of clinical outcome was based on post-transplant investigations as shown by: (1) post-transplant mechanical ventilation; (2) total hospital stay; (3) infectious morbidities (pneumonia, intra-abdominal abscess, central line sepsis, wound infection, and urinary tract infection); (4) acute and chronic rejection; (5) mortality (intensive care unit mortality, hospital mortality, 28-d mortality, and survival at one year post-transplant surveillance period).

These post-transplant parameters were investigated and documented daily during the patients’ post-transplant hospital stay and the period of one-year postoperative follow-up.

**Statistical analysis**

The results were expressed as mean ± SD. Data were analyzed using the SAS. Differences between means were evaluated using Student t test when normal distribution was confirmed by Shapiro-Wilks test. When the hypothesis of normal distribution was rejected, differences between groups were tested by nonparametric statistics using Mann-Whitney test for unpaired samples and Wilcoxon criterion for paired samples. Fisher’s exact test was used for analysis of categorical values when appropriate. A P value of < 0.05 was considered significant.

**RESULTS**

A total of 66 patients were enrolled in this study, including 33 patients in PN group and 33 patients in PUFA group. The mean age of the subjects was 51.6 years (range, 34-64 years). The clinical diagnosis of these patients included: hepatic cell carcinoma (27 cases), post-hepatitis B liver cirrhosis (35 cases), alcoholic liver cirrhosis (1 case), primary biliary liver cirrhosis (2 cases) and congenital poly cystic liver (1 case). Demographic and clinical data (including age, sex, clinical diagnosis, Child-Pugh classification of hepatic function, warm ischemic time, cold ischemic time, operative time, anhepatic phase and post-operative immunosuppression) are summarized in Table 1. With respect to warm ischemic time, cold ischemic time, operative time, anhepatic phase, ratio of Child-Pugh classification, immunosuppression and clinical diagnosis, there were no significant differences between the two groups in any of these above param-
Liver function assessment
No significant difference of pre-operative liver function was observed between the two groups. On days 2 and 9 after operation, a significant decrease of ALT (299.16 U/L ± 189.17 U/L vs 246.16 U/L ± 175.21 U/L, \( P = 0.024 \)) and PT (5.64 s ± 2.06 s vs 2.54 s ± 1.15 s, \( P = 0.035 \)) was seen in PUFA group compared with PN group. And there was no significant decrease of the following parameters tested on days 2 and 9: AST (116.31 U/L ± 42.19 U/L vs 121.09 U/L ± 53.14 U/L, \( P = 0.682 \)), TB (93.93 μmol/L ± 45.49 μmol/L vs 87.20 μmol/L ± 61.12 μmol/L, \( P = 1.439 \)), DB (42.74 μmol/L ± 17.36 μmol/L vs 36.22 μmol/L ± 21.63 μmol/L, \( P = 0.815 \)) and LDH (156.12 U/L ± 89.20 U/L vs 119.10 U/L ± 69.72 U/L, \( P = 1.112 \)) in PUFA group compared with PN group (Table 2).

Light microscopy
The histological examination after reperfusion revealed some swelling hepatocytes and inflammatory cell infiltration in the portal areas, and no significant difference of numerical score of portal inflammation was observed between the two groups.

Histological examination on day 9 in PN group revealed more inflammatory cells aggregating in hepatic sinusoid lumen, extensive swelling and some balloon-like degeneration of hepatocytes, extensive congestion, and bilirubin deposit in the hepatic plasma (Figure 2A). These were ameliorated markedly by parenteral nutritional support with omega-3 fatty acids (Figure 2B), and the numerical score of portal inflammation was significantly lowered in PUFA group (Table 3). There was no sign of acute rejection in both groups.

Clinical outcome
There was no significant difference of post-transplant mechanical ventilation between the two groups (\( P > 0.05 \)). Compared with PN group, the post-transplant hospital stay was significantly shortened in PUFA group (\( P < 0.05 \)). Infectious complications occurred in 6 cases of PN group (2 cases of pneumonia, 3 cases of intra-abdominal abscess and 1 case of urinary tract infection), and in 3 cases of PUFA group (2 cases of pneumonia, 1 case of intra-abdominal abscess). No acute or chronic rejection and hospital mortality were found in the two groups. All patients were followed up, and the one-year mortality in PN group was 9.1% (3/33), one died of pulmonary infection, one died of severe intra-hepatic cholangitis and hepatic dysfunction and the other of hepatic cell carcinoma recurrence. Only one patient in PUFA group (1/33, 3.1%) died of biliary complication and hepatic dysfunction during follow-up (Table 4).

DISCUSSION
An impairment of nutritional status is a frequent finding in patients with end-stage liver disease. Malnutrition adversely affects the prognosis of these patients and is associated with the morbidity and mortality after liver transplantation[16]. Malnutrition has been shown to be the only independent risk factor for the length of stay in the intensive care and the total number of days spent in the hospital, and the liver recipient’s nutritional status.
also influences the incidence of post-transplant complications and may therefore increase the costs of liver transplantation\[^{17,18}\]. After liver transplantation, surgical stress, postoperative fasting, and the possible occurrence of complications suggest the need for nutritional support. The primary goal of the nutritional support in the immediate post-transplant period is to provide adequate nutrition to promote recovery and replenishment of the depleted nutrient stores. Although most transplant centers use the similar post-transplant nutritional support as for other major abdominal operations, few studies have elucidated the role of postoperative nutritional support in the liver recipients.

Enteral nutrition is safer and less expensive than PN, and enteral nutrition has the potential advantage of maintaining intestinal trophism more effectively\[^{19}\]. This effect may help prevent bacterial translocation and enteric-origin infections in patients treated with transplantation\[^{20-26}\]. All patients in this study resumed their daily oral diet postoperatively as soon as bowel function returned to maintain intestinal trophism, but the recipients could not endure a large amount of liquid diet even with nasoenteric tube at the early phase after transplantation because of obvious abdominal pain, distention or diarrhea in our previous experience. The bowel function in all the patients in this study returned on day 3 or 4 after transplantation, and PN support discontinued on day 8 after surgery when the patients were able to maintain an adequate oral intake.

Omega-3 fatty acids mainly act as eicosapentaenoic acids (EPA) and docosahexaenoic acids (DHA), both had anti-inflammatory effects. EPA and DHA reduce the release of arachidonic acid-derived pro-inflammatory eicosanoids, and generate a group of lipid mediators called resolvins (E- and D-series) and protectins with potent anti-inflammatory and inflammation resolution properties\[^{22-24}\]. Studies with experimental models of liver reperfusion injury have reported the beneficial actions of n-3 PUFA-derived resolvins and protectins in preventing liver DNA damage and oxidative stress, thus significantly ameliorating the necroinflammatory liver injury and hepatic steatosis\[^{25-26}\]. The liver-protecting effects of postoperative PN support supplemented with omega-3 fatty acids were evaluated in this study. Liver enzyme of ALT released after I/R was significantly suppressed vs PN group. The results of histological examination on day 9 revealed that the hepaticocyte injury and inflammatory cell aggregation were ameliorated markedly in PUFA group. PUFA therapy could also decrease the infectious morbidities, and shorten the post-transplant hospital stay significantly. The possible mechanisms of omega-3 fatty acids include down-regulation of the inflammatory responses to surgery and immune modulation rather than a sole nutritional effect.

### Table 2 Effect of parenteral nutritional support with Omega-3 fatty acids on liver function

| Normal value | Group     | Day 1                | Day 2                | Day 9                | Decrease (Day 2-Day 9) |
|--------------|-----------|----------------------|----------------------|----------------------|------------------------|
| ALT (U/L)    | PN group  | 5.40 ± 1.17          | 4.03 ± 0.81          | 2.7 ± 0.4           | 0.4 ± 0.4              |
|              | PUFA group| 5.20 ± 0.80          | 3.92 ± 0.6           | 2.54 ± 0.4          | 0.4 ± 0.4              |
| AST (U/L)    | PN group  | 95.12 ± 61.79        | 82.16 ± 46.16        | 79.16 ± 45.44       | 2.54 ± 0.4             |
|              | PUFA group| 92.16 ± 52.95        | 80.25 ± 43.26        | 77.2 ± 42.16        | 2.54 ± 0.4             |
| TB (μmol/L)  | PN group  | 158.32 ± 65.41       | 140.25 ± 62.34       | 132.2 ± 60.22       | 2.54 ± 0.4             |
|              | PUFA group| 140.25 ± 62.34       | 128.25 ± 59.40       | 120.2 ± 57.41       | 2.54 ± 0.4             |
| DB (μmol/L)  | PN group  | 76.46 ± 31.28        | 68.25 ± 29.12        | 60.2 ± 27.01        | 2.54 ± 0.4             |
|              | PUFA group| 68.25 ± 29.12        | 60.2 ± 27.01         | 52.2 ± 25.01        | 2.54 ± 0.4             |
| LDH (U/L)    | PN group  | 47.39 ± 27.19        | 42.74 ± 17.36        | 38.12 ± 16.87       | 2.54 ± 0.4             |
|              | PUFA group| 42.74 ± 17.36        | 38.12 ± 16.87        | 33.62 ± 15.74       | 2.54 ± 0.4             |
| PT (s)       | PN group  | 17.16 ± 4.05         | 14.62 ± 3.87         | 12.17 ± 3.69        | 2.54 ± 0.4             |
|              | PUFA group| 14.62 ± 3.87         | 12.17 ± 3.69         | 10.85 ± 3.57        | 2.54 ± 0.4             |

PN: Parenteral nutrition; PUFA: Polyunsaturated fatty acid; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin; DB: Direct bilirubin; LDH: Lactate dehydrogenase; PT: Prothrombin time. *P < 0.05, †P < 0.01 vs day 2; ‡P < 0.05 vs PN group.

### Table 3 Effect of parenteral nutritional support with Omega-3 fatty acids on numerical score of portal inflammation

| Group     | Day 0 | Day 9 |
|-----------|-------|-------|
| PN group  | 5.5 ± 0.5 | 2.7 ± 0.9 |
| PUFA group| 5.2 ± 0.4 | 1.8 ± 0.6 |

PN: Parenteral nutrition; PUFA: Polyunsaturated fatty acid. *P < 0.05 vs PN group.

### Table 4 Effect of parenteral nutritional support with Omega-3 fatty acids on clinical outcome

| PN group | PUFA group |
|----------|------------|
| Post-transplant mechanical ventilation (h) | 12.1 ± 5.1 | 10.8 ± 5.4 |
| Post-transplant hospital stay (d) | 20.6 ± 4.6 | 18.7 ± 4.0† |
| Infectious morbidities | 6/33 | 3/33† |
| Acute/chronic rejection | 0/33 | 0/33 |
| ICU mortality | 0/33 | 0/33 |
| Hospital mortality | 0/33 | 0/33 |
| 28-d mortality | 0/33 | 0/33 |
| One-year mortality | 0/33 | 0/33 |

PN: Parenteral nutrition; PUFA: Polyunsaturated fatty acid; ICU: Intensive care unit. *P < 0.05 vs PN group.
Some of the patients exhibited an obvious nitrogen accumulation disorder reflected by either encephalopathy or an excessive rise in blood urea nitrogen in the immediate postoperative period. Branched-chain amino acids were chosen for this study because it can promote protein synthesis in patients with chronic liver diseases and avoid the additional metabolic load of transplanted liver\(^{23}\). Medium-chain triglycerides were included in the regimen to avert glucose intolerance and deposits in the transplanted liver. Based on the results of this study, we think that post-transplant nutritional support in the form of a solution enriched with branched-chain amino acids, dextrose, medium-chain triglycerides and omega-3 fatty acids might offer a benefit in terms of preserved liver function and better clinical outcome, including the decreased infectious morbidities and post-transplant hospital stay.

In conclusion, we have shown that omega-3 fatty acids-supplemented PN significantly improves the injury of transplanted liver, decreases the infectious morbidities, and shortens the post-transplant hospital stay.

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COMMENTS

Background

The liver recipients with liver insufficiency are known to experience a higher incidence of severe protein/calorie malnutrition, and malnutrition is associated with a greater risk of postoperative complications and mortality in patients undergoing liver transplantation. And ischemia/reperfusion injury associated with liver transplantation often leads to hepatic dysfunction despite the improvements in surgical techniques and perioperative medication.

Research frontiers

Omega-3 fatty acids exert anti-inflammatory and immunomodulatory properties through their ability to modulate the synthesis of different eicosanoids. Recent studies have described that supplementation with omega-3 fatty acids decreases the rate of inflammatory complication, the length of hospital stay, and the mortality after major abdominal surgeries.

Innovations and breakthroughs

Although most transplant centers use the similar post-transplant nutritional support as for other major abdominal operations, few studies have elucidated the role of postoperative nutritional support in the organ recipient. Based on the results of this study, the authors have shown that post-transplant nutritional support in the form of a solution enriched with branched-chain amino acids, dextrose, medium-chain triglycerides and omega-3 fatty acids might offer a benefit in terms of preserved liver function and better clinical outcome, including the decreased infectious morbidities and post-transplant hospital stay.

Applications

This study has shown that omega-3 fatty acids-supplemented parenteral nutrition (PN) significantly improves the injury of transplanted liver, decreases the infectious morbidities, and shortens the post-transplant hospital stay. The nutritional support strategy is recommended in patients undergoing liver transplantation.

Peer review

The manuscript evaluates the potential for supplementation with polyunsaturated fatty acid to ameliorate hepatic injury associated with reperfusion and PN. It provides evidences about an efficient nutritional support strategy for liver transplanted patients.

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