Fish oil-based lipid emulsion: current updates on a promising novel therapy for the management of parenteral nutrition-associated liver disease

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Abstract

Intestinal failure is characterized by loss of enteral function to absorb necessary nutrients and water to sustain life. Parenteral nutrition (PN) is a lifesaving therapeutic modality for patients with intestinal failure. Lifelong PN is also needed for patients who have short bowel syndrome due to extensive resection or a dysmotility disorder with malabsorption. However, prolonged PN is associated with short-term and long-term complications. Parenteral nutrition-associated liver disease (PNALD) is one of the long-term complications associated with the use of an intravenous lipid emulsion to prevent essential fatty acid deficiency in these patients. PNALD affects 30–60% of the adult population on long-term PN. Further, PNALD is one of the indications for isolated liver or combined liver and intestinal transplantation. There is no consensus on how to manage PNALD, but fish oil-based lipid emulsion (FOBLE) has been suggested to play an important role both in its prevention and reversal. There is significant improvement in liver function in those who received FOBLE as lipid supplement compared with those who received soy-based lipid emulsion. Studies have also demonstrated that FOBLE reverses hepatic steatosis and reduces markers of inflammation in patients on long-term PN. Future prospective studies with larger sample sizes are needed to further strengthen the positive role of FOBLE in PNALD.

Key words: intestinal failure; parenteral nutrition; parenteral nutrition-associated liver disease; fish oil-based lipid emulsion

Introduction

Intestinal failure is defined as the inability of enterocytes to absorb necessary nutrients, water, electrolytes, vitamins and minerals either due to reduced length of the intestine or loss of its normal function [1]. Further, intestinal failure patients secondary to short bowel syndrome suffer from gastric acid hypersecretion, pancreatic enzymes inactivation, rapid bowel transit, gallstone formation, renal calculi and liver dysfunction [2]. Parenteral nutrition (PN) is the lifesaving treatment modality for providing necessary nutritional support to patients with intestinal failure [3]. Nearly 40,000 patients in the United States are currently on PN for survival [3]. The length of PN therapy can range from short term to long term depending on the patient’s medical and nutritional needs [4]. Short-term (2–6 weeks) indications include post-operative support for patients whose bowel function has not returned to normal or pre-operative support for malnourished patients [4]. Patients requiring long-term

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Parenteral nutrition-associated liver disease

The incidence of PNALD in patients receiving long-term PN varies widely depending on the age group from 15–40% in adults and 40–60% in infants and neonates [8]. The prevalence of PNALD is greater in pediatric patients when compared with adults. The reasons for this are unknown [9]. Approximately 22% of deaths in patients on long-term PN are attributed to PNALD [10]. The clinical spectrum of hepatobiliary complications associated with PN range from steatosis, cholestasis, gallbladder sludge/stones, fibrosis and cirrhosis with significant overlap [11]. Patients with PNALD can present with either a single complication or a combination of complications [12]. Steatosis (defined as fat accumulation in the hepatocytes) can present as mild to moderate elevations in liver function tests and is usually benign. Cholestasis results from impaired secretion of bile and is associated with elevations in alkaline phosphatase, gamma glutamyl transferase and conjugated bilirubin. Both steatosis and cholestasis are reversible with termination of PN. Bile stasis can also occur in these patients due to reduced cholecystokinin secretion caused by lack of enteral stimulation, decreased bile flow and gallbladder contractility [13]. The causes of PNALD are multifactorial and can be divided into nutrition-related causes and non-nutrition-related causes (Table 1). Non-nutrient reversible causes such as sepsis and hepatotoxic medications should be actively sought and treated first before attributing the cause of elevated liver function tests to PNALD [13].

| Parenteral nutrition-related factors | Non-nutrient related factors | Factors exclusive to pediatric population | Factors affecting both adult and pediatric population |
|------------------------------------|-----------------------------|------------------------------------------|--------------------------------------------------|
| Duration of parenteral nutrition    | Prematurity                 | Recurrent septic episodes                |
| High calorie intake                | Low birth weight            | Lack of enteral stimulation or delayed initiation of enteral feeding |
| Lipid infusions > 1 g/kg/day       | Duration on antibiotics after bowel surgery in infants | Length of remaining small bowel |
| Cysteine and taurine deficiency    | Number of laparotomy surgeries in pediatric population | Underlying primary disease |
| Choline deficiency                 | Gastrochisis or jejunal atresia | Hepatotoxic medication |
| Manganese toxicity                 |                             |                                         |

Parenteral lipid emulsions: introduction and importance

Fats are esters of glycerol and fatty acids (FAs) [14]. FAs are hydrocarbon compounds with a methyl group at one end and a carboxyl group at the other end. FAs are usually classified as saturated and unsaturated FAs based on the absence or presence of double bonds, respectively [14]. Unsaturated FAs are further classified depending on the number of double bonds into mono-unsaturated fatty acids having only one double bond and polyunsaturated fatty acids (PUFAs) having more than a single double bond [15]. Further, fats are condensed non-carbohydrate calorie sources for the human body. FAs are also the principal structural components of cell membranes. They act as second messengers and ligands for nuclear receptors [15]. Long-chain PUFAs are also precursors for eicosanoids and various other compounds such as resolvins and neuroprotectins [16, 17]. Although, the human body synthesizes most of the FAs, some should be supplemented through diet. These are called essential fatty acids (EFAs).

To avoid EFA deficiency, exogenous EFAs, which include linoleic (LA), linolenic (α-LA), and arachidonic acids (AA), must be provided [17]. Of these, only LA is required since α-LA has no known function in humans [18]. Further, AA can be synthesized if LA is provided. Platelet function, wound healing, immunocompetence, prostaglandin synthesis and integrity of the skin and hair all require EFAs [18]. Prevention of EFA deficiency in patients with intestinal failure is most commonly accomplished by administering intravenous fat emulsions (IVFEs) in patients with short bowel syndrome [19].

PN formulations before the advent of IVFE consisted mainly of glucose and amino acids [20]. Complications of high dextrose load in addition to deficiency of essential FA led to incorporation of lipid emulsions into PN. Hence, IVFE was introduced in the 1960s to both prevent EFA deficiency and serve as a major source of non-protein calories [21]. Further, IVFE minimizes respiratory and metabolic stress and prevents fatty infiltration of the liver. Lipid (9 kcal/g) emulsions also provide more energy-rich source compared with glucose (3.4 kcal/g) and amino acids (4 kcal/g) [21]. The PN volume is reduced with the use of IVFE, which may be helpful for patients with fluid overload [22]. Although the time of development of EFA deficiency is variable and depends upon the patient’s nutritional status, nature of disease and age, biochemical EFA deficiency develops after 4 weeks of fat-free PN in hospitalized patients; patients on home PN, however, may not develop it for months after receiving fat-free PN [23]. The cause for this discrepancy is unknown. It has also been reported that neonates develop biochemical signs of EFA deficiency as early as the second day of life and within two
weeks of fat-free PN [24]. It is presently advised to start IVFE within seven days of starting PN to prevent EFA deficiency [23]. Daily requirements for EFA are unknown; however, studies have shown that EFA deficiency can be prevented by providing a minimum of 2–4% of total caloric intake as LA and 0.25–0.5% as α-LA [23].

The introduction of a successful IVFE in 1961 was one of the major advances in the administration of PN [25]. A cotton seed oil emulsion was the first IVFE (Lipomul) to be available in the United States, but it was immediately withdrawn from use due to adverse reactions including chills, fever, nausea, dyspnea, hypoxia, hypotension and fat embolism [25]. In the early 1960s, a soybean oil-based IVFE (Intralipid) was introduced and was well tolerated [26]. A study from Sweden reported that only eight patients developed a significant adverse reaction to an IVFE out of the 1.6 million units infused. Of those eight patients, only one adverse reaction was attributed to Intralipid infusion [26]. These results demonstrated the safety of soybean oil-based IVFE, which offered a source of EFA as well as an alternate calorie source to dextrose since complications of hyperosmolar glucose solutions, including liver steatosis, were increasingly recognized along with manifestations of fat-soluble vitamin deficiencies [27].

**Soybean oil-based lipid emulsion: its role in PNALD**

Historically, the IVFE was first derived from plant/vegetable oils because they are rich in EFAs [27]. The commercially available soybean oil-based lipid emulsion (SOBLE) products in the United States are intralipid-soybean oil emulsions based on, or a combination of, soybean and safflower oils (Liposyn) [27]. These contain LA and α-LA approximately in the proportion of 5:5:1 along with high content of phosphatidylcholine and low levels of α-tocopherol [28]. Both LA and α-LA have similar metabolisms with LA by its action on cholesterol 7 alpha hydroxylase, the rate-limiting enzyme in bile acid synthesis [37]. Further, FXR stimulates the transcription of the gut enterokine fibroblast growth factor 19, which mediates the repression of cholesterol 7 alpha-hydroxylase [37]. All of these mechanisms are involved in the pathogenesis of hepatobiliary dysfunction in patients with PNALD [38]. With the increasingly recognizable role of SOBLE in PNALD and other nutrition-related complications, IVFEs have evolved through generations by replacing n-6 PUFA with medium chain triglycerides (MCTs) or n-3 PUFA [38].

**Fish oil-based lipid emulsion: beneficial role in PNALD**

Fish oil, as a rich source of n-3 PUFA with lower phytosterol and alpha tocopherol content, is gaining popularity as an alternative source of IVFE in PN, either alone or in combination with others [39]. Further, FOBLE contains high concentrations of EPA and DHA, which are known to have anti-inflammatory properties [39]. They compete with AA and change the composition of cell membranes [40]. Additionally, hydrolyzed products of these membrane phospholipids modulate eicosanoid and cytokine biology [41]. Furthermore, they have a suppressive effect on cellular immunity including lymphocytes, neutrophil chemotaxis and T cells along with antigen presentation [41]. Hence, n-3 based IVFEs are finding their way as a combined nutritional and pharmacological agent for use in pro-inflammatory states such as sepsis and acute respiratory distress syndrome.

The beneficial effect of n-3 PUFA in inflammatory states has been demonstrated in a number of studies [42]. Liang et al. reported that colorectal cancer patients who received a mixed emulsion of FOBLE and SOBLE as a part of PN post-operatively for 7 days were found to have a significant decrease in serum IL-6 levels and increase in the CD4+ / CD8+ ratio [42]. Similarly, another study reported decreased levels of IL-1, IL-6, IL-10 and TNF-α in their patients who received n-3 PUFA-enriched PN post-operatively compared with those who received an isocaloric MCT/LCT (long-chain triglyceride) enriched PN [43]. Furthermore, Weiss et al. reported that perioperative administration of n-3 PUFA downregulated the inflammatory response favoring better outcomes in surgical trauma patients [44].

FOBLE has gained popularity in recent years for patients on PN with liver dysfunction, not only as a supplement for SOBLE but also as a therapeutic modality for reversal of PNALD [45]. The underlying mechanism for reversing liver dysfunction is not clearly known. Pscheidl et al. demonstrated in 2 distinct rat models studies an improved intestinal, portal perfusion and enhanced bactericidal defense of splanchnic circulation with FOBLE [46]. The lower pro-inflammatory properties of n-3 FA and decreased amounts of phytosterols in FOBLE compared with SOBLE are thought to play a role in the hepatoprotective nature of these emulsions [47].

Initially, the evidence for n-3 FA enriched IVFE reversing steatosis and cholestasis was demonstrated in animal model studies [48, 49]. Recently, studies have investigated the beneficial effect of FOBLE in pediatric and adult populations [50, 51]. One of the earlier studies conducted in two neonates with short bowel syndrome on PN reported reversal of liver disease after...
supplementation of n-3 PUFA [50]. Further, recent studies involving adult surgical and critically ill patients have demonstrated favorable response. A study involving patients who underwent major abdominal surgery reported improved liver functions in those who received FOBLE compared with those who received SOBLE [52]. Another study of gastrointestinal surgical patients receiving FOBLE in PN post-operatively reported improved liver functions compared with those receiving MCT/LCT combination [53]. Further, Mertes et al. found better liver tolerance in surgical and intensive care unit patients receiving a combination emulsion, SMOF (soybean oil, medium chain triglycerides, olive oil and fish oil) compared with those receiving SOBLE alone [54]. Additionally, one study of IF patients on PN for four weeks reported lower levels of liver enzymes in patients receiving SMOF compared with those receiving SOBLE [55]. Furthermore, a recent case report of an adult with PNALD by Burns et al. showed reversal of hepatic dysfunction with change of IVFE from soybean to FOBLE [56]. Jurewitch et al. demonstrated in their case report that n-3 enriched lipid emulsion (100% fish oil) normalized PN-induced cholestasis and resolved histochemical and ultrastructural abnormalities in an adult patient [57]. Concerns about the use of FOBLE monotherapy include the development of EFA deficiency and bleeding. One report described burn cell anemia in an infant receiving FOBLE monotherapy, which resolved with its discontinuation [58].

In summary, PNALD is a common complication of long-term PN that is in part due to the type and amount of IVFE. FOBLE has a lower amount of phytosterols and higher concentration of n-3 FA compared with SOBLE, which may prevent or potentially reverse PNALD. FOBLE may also have less pro-inflammatory effects, less immunosuppression and more antioxidant effects compared with standard SOBLE. Prolonged bleeding time, though rare, could be a drawback of fish oil use. Also, the currently available data on the clinical benefits of fish oil are based on a diverse group of patients. Future studies are needed to further strengthen the results of the promising role of FOBLE for prevention and treatment of PNALD in adults receiving long-term PN.

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References

1. O’Keefe SJ, Buchman AL, Fishbein TM et al. Short bowel syndrome and intestinal failure: consensus definitions and overview. Clin Gastroenterol Hepatol 2006;4:6–10.
2. Pironi L, Joly F, Forbes A et al. Long-term follow-up of patients on home parenteral nutrition in Europe: implications for intestinal transplantation. Gut 2011;60:17–25.
3. Goulet O and Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology 2006;130(2 Suppl 1): S16–28.
4. Andorsky DJ, Lund DP, Lilliehi CW et al. Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. J Pediatr 2001; 139:27–33.
5. Rhoda KM, Suryadevara S and Steiger E. Home parenteral nutrition support for intestinal failure. Surg Clin North Am 2011; 91:913–32.
6. Rhoda KM, Parekh NR, Lennon E et al. The multidisciplinary approach to the care of patients with intestinal failure at a tertiary care facility. Nutr Clin Pract 2010;25:183–91.
7. Kaufman SS, Atkinson JB, Bianchi A et al. Indications for pediatric intestinal transplantation: a position paper of the American Society of Transplantation. Pediatr Transplant 2001; 5:80–7.
8. Kelly DA. Intestinal failure-associated liver disease: what do we know today? Gastroenterology 2006;130(2 Suppl):S70–7.
9. Beath SV, Davies P, Papadopoulou A et al. Parenteral nutrition-related cholestasis in postsurgical neonates: multivariate analysis of risk factors. J Pediatr Surg 1996;31: 604–6.
10. Candusso M, Faraguna D, Sperli D et al. Outcome and quality of life in paediatric home parenteral nutrition. Curr Opin Clin Nutr Metab Care 2002;5:309–14.
11. Drongowski RA and Coran AG. An analysis of factors contributing to the development of total parenteral nutrition induced cholestasis. JPEN J Parenter Enteral Nutr 1989;13:586–9.
12. Luman W and Shaffer JL. Prevalence, outcome and associated factors of deranged liver function tests in patients on home parenteral nutrition. Clin Nutr 2002;21:337–43.
13. Cavicchi M, Beau P, Gremm P et al. Prevalence of liver disease and permanent intestinal failure. Ann Intern Med 2000;132: 525–32.
14. Simopoulos AP. Essential fatty acids in health and chronic disease. Am J Clin Nutr 1999;70(Suppl):S605–S695.
15. Das UN. Essential Fatty acids - a review. Curr Pharm Biotechnol 2006;7:467–82.
16. Holman RT, Johnson SB and Hatch TF. A case of human linolenic acid deficiency involving neurological abnormalities. Am J Clin Nutr 1982;35:617–23.
17. Lowe NJ and DeQuoy PR. Linoleic acid effects on epidermal DNA synthesis and cutaneous prostaglandin levels in essential fatty acid deficiency. J Invest Dermatol 1978;70:200–3.
18. Uauy R, Peizano P, Hoffman D et al. Role of essential fatty acids in the function of the developing nervous system. Lipids 1996;31:S167–76.
19. Lands B. Consequences of essential fatty acids. Nutrients 2012;4:1338–57.
20. Calder PC, Jensen GL, Koletzko BV et al. Lipid emulsions in parenteral nutrition of intensive care patients: current thinking and future directions. Intensive Care Med 2010;36: 735–49.
21. Pittiruti M, Hamilton H, Biffi R et al. ESPEN Guidelines on Parenteral Nutrition: central venous catheters (access, care, diagnosis and therapy of complications). Clin Nutr 2009;28: 365–77.
22. Mirtallo J, Canada T, Johnson D et al. Safe Practices for Parenteral Nutrition. JPEN J Parenter Enteral Nutr 2004;28: S39–70.
23. Mascioli EA, Lopes SM, Champagne C et al. Essential fatty acid deficiency and home total parenteral nutrition patients. Nutrition 1996;12:245–9.
24. American Academy of Pediatrics Committee on Nutrition. Nutritional needs of low-birth-weight infants. Pediatrics 1985; 76:976–86.
25. Adolph M. Lipid emulsions in parenteral nutrition. Ann Nutr Metab 1999;43:1–13.
26. Shenkin A and Wretlind A. Parenteral nutrition. World Rev Nutr Diet 1978;28:1–111.
27. Shaffer JL and Black PC. Immune modulation by parenteral lipid emulsions. Am J Clin Nutr 2007;85:1171–84.
28. Shaffer J. An update on parenteral lipids and immune function: only smoke, or is there any fire? Curr Opin Clin Nutr Metab Care 2006;9:79–83.
29. Lewis RA. Interactions of eicosanoids and cytokines in immune regulation. Adv Prostaglandin Thromboxane Leukot Res 1990;20:170–8.
30. Tilley SL, Coffman TM and Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. J Clin Invest 2001;108:15–23.

31. Heller A, Koch T, Schmeck J et al. Lipid mediators in inflammatory disorders. Drugs 1998;55:487–96.

32. Serhan CN, Arita M, Hong S et al. Resolvins, docosatrienes, and neuroprotectins, novel omega-3-derived mediators, and their endogenous aspirin-triggered lipids. Lipids 2004;39:1125–32.

33. Kosters A and Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. Semin Liver Dis 2010;30:186–94.

34. Beckh K, Kneip S and Arnold R. Direct regulation of bile secretion by prostaglandins in perfused rat liver. Hepatology 1994;19:1208–13.

35. Colomb V, Jobert-Giraud A, Lacaille F et al. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. JPEN J Parenter Enteral Nutr 2000;24:345–50.

36. Lauriti G1, Zani A, Aufieri R et al. The role of FXR in disorders of bile acid homeostasis. Physiology 2008;23:285–95.

37. Eloranta JJ and Kullak-Ublick GA. The role of FXR in disorders of bile acid homeostasis. Physiology 2008;23:285–95.

38. Tillman EM. Review and clinical update on parenteral nutrition-induced cholestasis in newborn piglets. Pediatr Res 1999;45:202–8.

39. Meisel JA, Le HD, de Meijer VE et al. Comparison of 5 intravenous lipid emulsions and their effects on hepatic steatosis in a murine model. J Pediatr Surg 2011;46:666–73.

40. Gura KM, Duggan CP, Collier SB et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:e197–201.

41. Gura KM, Lee S, Valin C et al. Safety and efficacy of a fish oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678–86.

42. Heller AR, Rössel T, Gottschlich B et al. Omega-3 fatty acids improve liver and pancreas function in postoperative cancer patients. Int J Cancer 2004;111:511–6.

43. Wang J, Yu JC, Kang WM et al. Superiority of a fish oil-enriched emulsion to medium-chain triacylglycerols/long-chain triacylglycerols in gastrointestinal surgery patients: a randomized clinical trial. Nutrition 2012;28:623–9.

44. Mertes N, Grimm H, Fürst P et al. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. Ann NutrMetab 2006;50:253–9.

45. Mayer K, Gokorsch S, Fegbeutel C et al. Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med 2003;167:1321–8.

46. Pscheidl EM, Schwyalsky M, Tshaikowsky K et al. Fish oil-supplemented parenteral diets normalize splanchnic blood flow and improve killing of translocated bacteria in a low-dose endotoxin rat model. Crit Care Med 2000;28:1489–96.

47. Pscheidl EM, Wan JM, Blackburn GL et al. Influence of omega-3 fatty acids on splanchnic blood flow and lactate metabolism in an endotoxemic rat model. Metabolism 1992;41:698–705.

48. Van Aerde JE, Duerksen DR, Gramlich L et al. Intravenous fish oil emulsion attenuates total parenteral nutrition-induced cholestasis in newborn piglets. Pediatr Res 1999;45:202–8.

49. Lauriti G1, Zani A, Aufieri R et al. The role of inflammation in cholestasis: clinical and basic aspects. Semin Liver Dis 2010;30:186–94.

50. Duggan CP, Collier SB et al. Reversal of parenteral nutrition-associated liver disease in two infants with short bowel syndrome using parenteral fish oil: implications for future management. Pediatrics 2006;118:e197–201.

51. Gura KM, Lee S, Valin C et al. Safety and efficacy of a fish oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics 2008;121:e678–86.

52. Mayer K, Gokorsch S, Fegbeutel C et al. Parenteral nutrition with fish oil modulates cytokine response in patients with sepsis. Am J Respir Crit Care Med 2003;167:1321–8.

53. Pscheidl EM, Schwyalsky M, Tshaikowsky K et al. Fish oil-supplemented parenteral diets normalize splanchnic blood flow and improve killing of translocated bacteria in a low-dose endotoxin rat model. Crit Care Med 2000;28:1489–96.

54. Pscheidl EM, Wan JM, Blackburn GL et al. Influence of omega-3 fatty acids on splanchnic blood flow and lactate metabolism in an endotoxemic rat model. Metabolism 1992;41:698–705.

55. Jurewitsch B, Gardiner G, Naccarato M et al. Four-week parenteral nutrition-induced cholestasis in newborn piglets. Pediatr Res 1999;45:202–8.

56. Burns DL and Gill BM. Reversal of parenteral nutrition-associated liver disease with a fish oil-based lipid emulsion (Omegaven) in an adult dependent on home parenteral nutrition. JPEN J Parenter Enteral Nutr 2013;37:274–80.

57. Jurewitsch B, Gardiner G, Naccarato M et al. Omega-3-enriched lipid emulsion for liver salvage in parenteral nutrition-associated cholestasis in the adult patient. JPEN J Parenter Enteral Nutr 2011;35:386–90.

58. Mallah HS, Brown MR, Rossi TM et al. Parenteral fish oil-associated burr cell anemia. J Pediatr 2010;156:324–6.