HHS Public Access

Author manuscript

Am J Surg. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

Am J Surg. 2017 October ; 214(4): 733–737. doi:10.1016/j.amjsurg.2016.10.026.

Risk of Post-Procedural Bleeding in Children on Intravenous Fish Oil

Prathima Nandivada, MD[a,*], **Lorenzo Anez-Bustillos, MD**[a,*], **Alison A. O'Loughlin, MEd**[a], **Paul D. Mitchell, MSc**[b], **Meredith A. Baker, MD**[a], **Duy T. Dao, MD**[a], **Gillian L. Fell, MD PhD**[a], **Alexis K. Potemkin, BSN**[a], **Kathleen M. Gura, PharmD**[c], **Ellis J. Neufeld, MD PhD**[d], and **Mark Puder, MD PhD**[a]

[a]Vascular Biology Program and the Department of Surgery, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts, 02115 USA

[b]Clinical Research Center, Biostatistics Core, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts, 02115 USA

[c]Department of Pharmacy, Boston Children's Hospital, 300 Longwood Avenue, Boston, Massachusetts, 02115 USA

[d]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, 300 Longwood Avenue, Boston, Massachusetts, 02115 USA

Abstract

Background—Intestinal failure-associated liver disease (IFALD) can be treated with parenteral fish oil (FO) monotherapy, but practitioners have raised concerns about a potential bleeding risk. This study aims to describe the incidence of clinically significant post-procedural bleeding (CSPPB) in children receiving FO monotherapy.

Methods—A retrospective chart review was performed on patients at our institution treated with intravenous FO for IFALD. CSPPB was defined as bleeding leading to re-operation, transfer to the intensive care unit, re-admission, or death, up to one month after any invasive procedure.

Results—From 244 patients reviewed, 183 underwent ≥1 invasive procedure (n=732). Five (0.68%, 95% CI 0.22–1.59%) procedures resulted in CSPPB. FO therapy was never interrupted. No deaths occurred.

Conclusions—Findings suggest that FO therapy is safe, with a CSPPB risk no greater than that reported in the general population. O3FA should not be held in preparation for procedures or in the event of bleeding.

Keywords

Fish oil; omega-3 fatty acids; intestinal failure-associated liver disease; post-procedure bleeding

Corresponding Author: Mark Puder, MD, PhD, 300 Longwood Avenue, Fegan 3, Boston, MA 02115, Phone: 617-355-1838, Fax: 617-730-0477, mark.puder@childrens.harvard.edu.

*Contributed equally to this manuscript

INTRODUCTION

Intravenous fish oil (FO)-based lipid emulsions are used in place of soybean oil-derived emulsions for the treatment of intestinal failure-associated liver disease (IFALD)[1]. FO emulsions are rich in omega-3 fatty acids (O3FA), mainly docosahexaenoic and eicosapentaenoic acids (DHA and EPA, respectively). Eicosanoids and prostanoids derived from O3FA are anti-inflammatory mediators and are known to have important vascular and hemostatic effects[2]. The effects of EPA and DHA on platelet aggregation, coagulation, and other rheological properties of blood have been extensively addressed in the literature. O3FA may have beneficial effects in several clinical situations. Despite these effects, the hematologic attributes of FO have raised concern for an increased risk of bleeding in patients administered O3FA-rich compounds.

The hemostatic effects of O3FA are reflected in ex-vivo platelet function tests. EPA and DHA can significantly reduce platelet aggregation and activation based on results from aggregometry assays in humans[3], thromboelastography, and thromboelastography platelet mapping in a neonatal piglet model[4]. Increased bleeding time has also been reported, although not consistently[5]. Nonetheless, a direct link has not been established between the theoretical risk and *ex-vivo* studies, to an increased bleeding risk *in-vivo* with O3FA. Results from numerous randomized clinical trials and epidemiological studies have failed to find an association between O3FA and bleeding[5–7]. Additionally, studies addressing the use of FO supplementation in different clinical settings have failed to show an increased risk of bleeding through assessment of secondary outcomes or adverse events[5]. This holds true even in studies in which patients received FO in addition to other antiplatelet agents or anticoagulants[8,9]. Regardless, on the basis of the theoretical risk, surgeons and anesthesiologists still often recommend discontinuing FO therapy in preparation for invasive procedures.

FO was first used as monotherapy in the treatment of essential fatty acid deficiency (EFAD) in a parenteral nutrition (PN)-dependent adolescent with a soy allergy 14 years ago[10]. Since that index case, more than 240 patients have received treatment with FO emulsions as monotherapy for IFALD at our institution. The use of intravenous FO therapy for IFALD was associated with decreased mortality and the need for liver and multi-visceral transplantation. Short bowel syndrome is a common underlying diagnosis in the PN-dependent pediatric population that leads to the need for multiple invasive procedures and surgeries during childhood. A typical child with intestinal failure undergoes a median of four invasive abdominal procedures and highlights the importance of accurately defining the potential risk of FO-associated bleeding[11]. The goal of this report is to describe the incidence of clinically significant post-procedural bleeding (CSPPB) in pediatric patients receiving parenteral FO monotherapy for the treatment of IFALD.

METHODS

Study Population

A retrospective chart review of prospectively enrolled patients was performed on patients receiving intravenous FO (Omegaven®, Fresenius-Kabi AG, Bad Homburg, Germany) for

the treatment of IFALD at Boston Children's Hospital. This treatment was administered under a compassionate use protocol (IND# 73488). Ascertainment of the patient population was assured to be complete as all patients were prospectively enrolled to receive the treatment. IFALD was defined as a direct bilirubin greater than 2 mg/dL (34.2 μmol/L) in the absence of other diagnoses of liver disease. Inclusion criteria for the current study comprised patients who underwent any type of invasive procedure between September 2004 and July 2015. Invasive procedures were defined as those violating a vascularized and/or epithelialized surface. Procedures were categorized based on the body site involved. Those performed simultaneously at different body sites were considered separately. Vascular access procedures were included only if a tunneling and/or cut-down technique for device insertion was performed. Vascular percutaneous interventions were not considered for this study. Endoscopic procedures were included only if involving transgression of mucosal surfaces (i.e., biopsies). Intravenous FO was infused intravenously at a dose of 1 g/kg/day over 8–24 hours. Exclusion criteria included patients in the database that had not undergone any type of invasive procedure while receiving intravenous FO.

Peri-procedural Data Collection

Laboratory values obtained within one month of each procedure were recorded. These values included complete blood count, coagulation profile, liver enzymes, direct bilirubin, fatty acid profiles, and the duration of FO therapy at the time of the procedure. In patients that underwent multiple tests prior to a procedure, values obtained from those performed closest to the date of procedure were recorded. Fatty acid profiles include levels of linoleic acid, alpha-linolenic acid, arachidonic acid (ARA), EPA, DHA; total amounts of saturated, mono- and poly-unsaturated, omega-3, and omega-6 fatty acids; and triene to tetraene ratio, the biochemical marker of EFAD which is defined as a ratio ≥ 0.2.

Study End-Point

A definition for CSPPB was established based on the presence of at least one of the following within one month after an invasive procedure: (1) need for re-exploration or return to the operating room due to bleeding; (2) need for transfer to intensive care unit due to bleeding; (3) need for visit to emergency department or re-admission to the hospital for treatment of bleeding complications; or (4) death as a result of significant bleeding.

Statistical Analyses

Patient and procedure characteristics are presented as frequency (percentage) when categorical and median (interquartile range, IQR) when continuous, as none of the latter were normally distributed. For 35 procedures in 21 subjects, preoperative direct bilirubin levels <0.1 were recoded to 0.1 mg/dL. All analyses were accomplished with SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

Charts from 244 patients given intravenous FO for the treatment of IFALD were reviewed. Of these, 183 (75%) underwent at least one invasive procedure. There were 732 total invasive procedures among the 183 patients. Patients were 39.9% female and had a median

age of 3 months at the time of FO therapy initiation and 10.1 months at the time of the procedure (Tables 1 and 2). Among the invasive procedures included in this study, 42.9% were related to vascular access, 28.6% were abdominal, and 14.3% pertained to invasive endoscopic procedures (Table 2). Pre-procedural fatty acid analyses reflected values that are typically seen in patients receiving intravenous FO, with a median omega-3:omega-6 fatty acid ratio of 1.4 (IQR 1.0-1.9) (Table 3).

Five out of the 732 procedures (0.68%; CI 0.22%–1.59%) resulted in CSPPB. Of these, 3 were of gastrointestinal origin. The first event occurred following a small bowel resection on a 5-year-old male patient with esophageal varices and gastropathy from portal hypertension. The patient required transfer to the intensive care unit on post-operative day 21 due to active bleeding from his stoma which ceased following the application of pressure. Upper endoscopy failed to reveal a bleeding source and, 6 days later, a small bleeding vessel at the ileostomy site was identified and controlled at the bedside. The second case of lower gastrointestinal bleeding occurred in a 10-year-old male following the takedown of a jejunostomy that initially required transfer to the intensive care unit. He later returned to the operating room for an exploratory laparotomy and push enteroscopy. Although a true source of bleeding was not found, the intervention allowed for the identification of two questionable areas of friable mucosa at the anastomosis which were oversewn. The third event occurred in a 10-month-old female who was coagulopathic (INR 1.69) with severe portal hypertension from end-stage liver disease who presented with recalcitrant bleeding from her stoma. She required a return to the operating room for stoma closure after failed initial cauterization and suture ligation of stomal site bleeding of friable granulation tissue. The patient succumbed on post-operative day 9, having had an exploratory laparotomy two days prior for washout and repair of an anastomotic leak. Although the patient had persistent consumptive coagulopathy and oozing from multiple sites, her death was not considered to be due to post-operative bleeding but to sepsis and multiorgan system failure.

The other two cases were related to complications from procedures for establishing vascular access. One case involved a 12-month-old female during a failed attempt for cut-down placement of an internal jugular central venous catheter. An expanding neck hematoma was noticed upon awakening in the operating room and the patient was promptly re-anesthetized for cervical exploration. Intraoperative findings included an oozing defect in the sidewall of a small vessel feeding into the internal jugular vein adjacent to the repaired venotomy from the failed attempt. This was subsequently ligated. Of note, the patient had been on systemic anticoagulation since 4 months prior to surgery due to an episode of deep vein thrombosis. The other event occurred in a 14-month-old male who underwent replacement of a tunneled central venous catheter given mechanical complications with the device. Upon awakening, there was evidence of a hematoma at the tunnel site that was controlled uneventfully by holding pressure. The patient was admitted overnight for observation and discharged on post-operative day 1. Intravenous FO therapy was not interrupted for any of the reported events.

No patterns predicting the development of CSPPB among patients receiving parenteral FO were identified. No deaths due to bleeding occurred. Seven of 183 patients died within one

month of their procedure from causes that were unrelated to CSPPB, but rather sepsis, respiratory failure, and/or multiorgan system failure.

Eight particular cases with peri-procedural bleeding episodes were excluded as they were not considered to be a complication of the procedure. One of these episodes occurred in a 3-year-old female with history of intestinal transplantation who was admitted to the hospital for bloody output from her gastrostomy tube, although the insertion site appeared clean and dry. The patient had undergone excision of granulation tissue around the tube four days prior to her presentation. In another case, a 15-month-old female experienced multiple bleeding episodes likely from granulation tissue at her gastrostomy site, the first of which occurred 7 days after undergoing an esophagogastroduodenoscopy (EGD) with biopsies. Another 2-year-old male patient presented multiple times to the emergency department with small amounts of blood in loose stool more than 2 weeks after an exploratory laparotomy with extensive lysis of adhesions, cholecystectomy, and primary repair of a single iatrogenic enterotomy. The patient was admitted on two occasions mostly for concomitant fever requiring workup, and not necessarily for the bloody stools. Four other patients with episodes of persistent bloody stools required admission to the hospital, all of them following colonoscopy and EGD with biopsies as part of the workup for lower gastrointestinal bleeding. All of these patients were later found to have eosinophilic enteropathy and/or milk protein allergy. Similarly, one 4-year-old male was admitted on post-procedure day 1 of an EGD with biopsies for multiple episodes of emesis, one of them bloody, and fever. Once again, admission was mostly driven by the sepsis workup, and not the single, self-resolved episode of bloody emesis.

DISCUSSION

Results from this retrospective clinical review demonstrated an incidence of CSPPB of less than 1% in children with IFALD treated with long-term intravenous FO monotherapy. These findings support those from prior studies showing that *ex-vivo* hemostatic effects of O3FA supplementation do not necessarily translate into a clinically significant increased risk of bleeding[5]. Greenland Eskimos, for example, who base their diets on seafood products rich in O3FA, have prolonged bleeding times and mild bleeding tendencies that have never been described as clinically dangerous[12].

The hemostatic effects of EPA and DHA are multifactorial. ARA is the most common precursor of prostaglandin synthesis. O3FA inhibit platelet aggregation by decreasing the production of thromboxane A_2, a pro-aggregatory derivative of ARA, and favor the formation of thromboxane A_3, an anti-aggregatory derivative of DHA[13,5,14]. FO has also been shown to decrease platelet count, although a concomitant increase in platelet size seems to keep the platelet mass unchanged[15]. In endothelial cells, synthesis of prostaglandin I_3, an inhibitor of platelet aggregation, is favored by the displacement of ARA by EPA[16,17]. Changes induced by O3FA at the membrane and intracellular levels also lead to inhibited platelet function through augmentation of the negative surface charge density, modulation of signal-transduction molecules, and decreased adhesiveness and granule secretion[5,18–20]. The inhibitory effect of O3FA on pro-coagulant platelet- and monocyte-derived microparticles has also been described in specific situations[21,22]. Additionally, EPA and DHA can decrease

platelet-mediated thrombin generation, thereby acting indirectly on the coagulation cascade[23]. O3FA are also known to potentiate plasma fibrinolysis by increasing the levels of vascular plasminogen activator and reducing the levels of its inhibitors[24]. It is this combination of effects of O3FA that give them a role as cardioprotective molecules.

Reports by Bays[6], supported by the expert opinions of Harris[7], and more recently by Wachira et al[5], summarize available studies that provide direct and indirect evidence that O3FA do not increase the risk of clinically significant bleeding, even in patients receiving antiplatelet or anticoagulation medications. Nonetheless, in the same report, Bays[6] proposed recommendations to healthcare professionals regarding the safety of FO therapy. Included among his recommendations was that O3FA supplementation “should probably be discontinued during acute bleeding episodes.” It is evident that regardless of the clinical data, there is still some skepticism regarding the safety of O3FA in the peri-operative setting. Von Schaky et al[25] studied the incorporation and metabolism of EPA and DHA in humans supplemented with an O3FA-rich diet. Interestingly, the levels of DHA in erythrocyte membranes had not returned to baseline even 20 weeks after cessation of FO supplementation. As expected, platelet aggregation was persistently decreased while on FO, returning to baseline at the end of the study period, nearly 20 weeks after stopping treatment. Based on these findings, the peri-operative discontinuation of FO supplementation often recommended by surgeons and anesthesiologists should have minimal to no effect on the levels of fatty acids present and stored in cell membranes at the time of the procedure.

Data addressing the peri-operative use of FO therapy in children is quite limited. Before the introduction of parenteral FO for the treatment and reversal of IFALD, there was no established clinical indication for the use of FO emulsions in children. Although the efficacy and safety of FO administration was described by Gura et al[26], isolated case reports of adverse bleeding effects, supported by the theoretical concern, have guided practice preferences of certain groups and institutions. Dicken et al[4], for example, recently reported the case of a 9-month-old infant with no history of bleeding diathesis, who developed a “life-threatening hemorrhage following a standard central venous catheter change” while receiving FO monotherapy for IFALD. Bleeding reportedly stopped three days following discontinuation of parenteral FO. This led the authors to establish a causal relationship between the administration of the FO and the occurrence of the bleeding event. As a result of this single episode, the authors’ institution now recommends discontinuing parenteral FO therapy 72 hours pre-operatively in high-risk cases. Unfortunately, the authors did not report whether other plausible causes of coagulopathy were excluded as part of the workup, such as investigation into the extent of intrinsic liver injury in a child with IFALD, or a sepsis workup in the setting of an indwelling central venous catheter. Their follow-up study in piglets reported thromboelastography as the sole hemostatic parameter tested. There were no clinically significant hemorrhagic events in these animals.

Our institution’s experience with the use of intravenous FO which spans more than a decade has allowed us to provide this therapy to more than 240 children with IFALD. Although this indication is yet to be approved by the United States Food and Drug Administration, patients are able to receive the medication under a compassionate use protocol. To our knowledge, the incidence of peri-procedural bleeding in such a large cohort of pediatric patients

receiving intravenous FO has never been reported. The 0.68% incidence of CSPPB falls below that reported in other settings in the pediatric population[27,28].

Of all the cases reviewed, 113 involved creation of a gastrointestinal anastomosis. Only one of these (0.88%) resulted in the described event of CSPPB. The incidence of bleeding in this review is therefore below the average 4% that has been reported in adults in other series not using FO[29–33]. However, reports available in the literature oftentimes account for all types of bleeding events, including those managed conservatively and where bleeding stops spontaneously. When only considering events that require intervention, such as the one we described, the incidence drops to about 1%[29]. As for stoma bleeding following its creation, the incidence in this review was 1.96% and fell within the range of 0.7%–10% that is reported elsewhere in the pediatric literature[34–36].

The retrospective nature of this review is a limitation of this study. Ideally, a randomized controlled trial would provide a more robust assessment. The present review is limited to findings of patients receiving extremely high doses of FO with preexisting liver disease treated in a single institution. This can potentially compromise the generalizability of a relatively low risk of peri-procedural bleeding. The need for blood transfusions (either intra- or post-operatively) was not used to define bleeding events given the lack of established criteria for transfusion at our institution. In addition, blood transfusions are one of the most overused hospital procedures in the United States and practice patterns for transfusion are known to be highly variable among pediatric critical care practitioners[37,38]. Similarly, we did not include cases where, according to the operative reports, significant intraoperative bleeding was encountered and adequately controlled, as interpretation of these events is not standardized and is highly variable and subjective among the many surgeons in our department. Additionally, intraoperative bleeding may reflect instances of vessel injury rather than coagulopathy or alteration of other bleeding parameters.

Regardless of these limitations, the administration of intravenous FO emulsions at a dose of 1 g/kg/day in patients with liver injury should be considered the extreme model of exposure to O3FA. To put this dose in perspective, an average 70-kg male on oral FO supplementation will take 1 g per day for cardioprotection as recommended by the American Heart Association, or 3–5 g per day for the treatment of hypertriglyceridemia[39]. This amounts to a dose of 14–71 mg/kg/day. These numbers drop even further when accounting for the enteral bioavailability of O3FA[40]. The finding that no significantly increased risk of bleeding was observed, even when given at such high doses, should eliminate this misconception.

Based on these results, it appears that the benefits of an indicated invasive intervention outweigh the theoretical risk of bleeding in patients on intravenous FO therapy. To add to this is the potential harmful effect that could result from peri-procedural withholding of lipids in PN-dependent children with significant malnutrition. As new lipid emulsions combining plant-based and fish oils are on the horizon in the United States, we may experience an increased population of PN-dependent patients receiving intravenous FO therapy, either as monotherapy or in combination with other fat sources.

While hemostatic changes with FO therapy exist, results from this study show that these did not translate into an increased risk of clinically significant bleeding. FO lipid emulsion therapy may continue to be offered to PN-dependent children with IFALD and there is little evidence to withhold it in preparation for invasive procedures.

Acknowledgments

Research funding is provided by the Boston Children's Hospital Surgical Foundation and the Vascular Biology Program within Boston Children's Hospital (LA-B, AAO, DTD, MAB, GLF, and MP), the Joshua Ryan Rappaport Fellowship (PN), the Corkin and Maher Family Fund, and the National Institutes of Health Grants 5T32HL007734-22 (MAB), and 1F32DK104525-01 (GLF). All authors reviewed the article and were involved in the final approval of version to be published.

References

1. Puder M, Valim C, Meisel JA, Le HD, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition-associated liver injury. Ann Surg. 2009 Sep; 250(3):395–402. [PubMed: 19661785]
2. Leaf A, Weber PC. Cardiovascular effects of n-3 fatty acids. N Engl J Med. 1988 Mar 3; 318(9): 549–57. [PubMed: 3277056]
3. Gao L, Cao J, Mao Q, Lu X, et al. Influence of omega-3 polyunsaturated fatty acid-supplementation on platelet aggregation in humans: a meta-analysis of randomized controlled trials. Atherosclerosis. 2013 Feb; 226(2):328–34. [PubMed: 23153623]
4. Dicken BJ, Bruce A, Samuel TM, Wales PW, et al. Bedside to bench: The risk of bleeding with parenteral omega-3 lipid emulsion therapy. J Pediatr. 2014 Mar; 164(3):652–4. [PubMed: 24321533]
5. Wachira JK, Larson MK, Harris WS. n-3 Fatty acids affect haemostasis but do not increase the risk of bleeding: clinical observations and mechanistic insights. Br J Nutr. 2014 May; 111(9):1652–62. [PubMed: 24472372]
6. Bays HE. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol. 2007 Mar 19; 99(6A):35C–43C.
7. Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am J Cardiol. 2007 Mar 19; 99(6A):44C–46C.
8. Gajos G, Rostoff P, Undas A, Piwowarska W. Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) st. J Am Coll Cardiol. 2010 Apr 20; 55(16):1671–8. [PubMed: 20394870]
9. Cairns JA, Gill J, Morton B, Roberts R, et al. Fish oils and low-molecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angioplasty. The EMPAR Study. Circulation. 1996 Oct 1; 94(7):1553–60. [PubMed: 8840843]
10. Gura KM, Parsons SK, Bechard LJ, Henderson T, et al. Use of a fish oil-based lipid emulsion to treat essential fatty acid deficiency in a soy allergic patient receiving parenteral nutrition. Clin Nutr. 2005 Oct; 24(5):839–47. [PubMed: 16029913]
11. Khan FA, Mitchell PD, Fisher JG, Sparks EA, et al. Magnitude of surgical burden associated with pediatric intestinal failure: a multicenter cohort analysis. J Pediatr Surg. 2014 Dec; 49(12):1795–8. [PubMed: 25487486]
12. Simopoulos AP. Summary of the conference on the health effects of polyunsaturated fatty acids in seafoods. J Nutr. 1986 Dec; 116(12):2350–4. [PubMed: 3806233]
13. Thorngren M, Gustafson A. Effects of 11-week increase in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation. Lancet. 1981 Nov; 318(8257):1190–3.
14. Dyerberg J. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet. 1978 Jul; 312(8081):117–9.
15. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. Am J Clin Nutr. 1991 Sep; 54(3):438–63. [PubMed: 1908631]

16. Moncada S, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. Nature. 1976 Oct 21; 263(5579):663–5. [PubMed: 802670]
17. Goodnight SH, Harris WS, Connor WE. The effects of dietary omega 3 fatty acids on platelet composition and function in man: a prospective, controlled study. Blood. 1981 Nov; 58(5):880–5. [PubMed: 7295999]
18. Li XL, Steiner M. Fish oil: a potent inhibitor of platelet adhesiveness. Blood. 1990 Sep 1; 76(5): 938–45. [PubMed: 2118400]
19. Cohen MG, Rossi JS, Garbarino J, Bowling R, et al. Insights into the inhibition of platelet activation by omega-3 polyunsaturated fatty acids: beyond aspirin and clopidogrel. Thromb Res. 2011 Oct; 128(4):335–40. [PubMed: 21621252]
20. Larson MK, Shearer GC, Ashmore JH, Anderson-Daniels JM, et al. Omega-3 fatty acids modulate collagen signaling in human platelets. Prostaglandins Leukot Essent Fatty Acids. Jan; 84(3–4):93–8.
21. Del Turco S, Basta G, Lazzerini G, Evangelista M, et al. Effect of the administration of n-3 polyunsaturated fatty acids on circulating levels of microparticles in patients with a previous myocardial infarction. Haematologica. 2008 Jun 1; 93(6):892–9. [PubMed: 18469350]
22. Phang M, Lincz L, Seldon M, Garg ML. Acute supplementation with eicosapentaenoic acid reduces platelet microparticle activity in healthy subjects. J Nutr Biochem. 2012 Sep; 23(9):1128–33. [PubMed: 22137256]
23. Larson MK, Tormoen GW, Weaver LJ, Luepke KJ, et al. Exogenous modification of platelet membranes with the omega-3 fatty acids EPA and DHA reduces platelet procoagulant activity and thrombus formation. Am J Physiol Cell Physiol. 2013 Feb 1; 304(3):C273–9. [PubMed: 23174566]
24. Barcelli U, Glas-Greenwalt P, Pollak VE. Enhancing effect of dietary supplementation with omega-3 fatty acids on plasma fibrinolysis in normal subjects. Thromb Res. 1985 Aug 1; 39(3): 307–12. [PubMed: 2996169]
25. von Schacky C, Fischer S, Weber PC. Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. J Clin Invest. 1985 Oct; 76(4):1626–31. [PubMed: 2997286]
26. Gura KM, Lee S, Valim C, Zhou J, et al. Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. Pediatrics. 2008 Mar 1; 121(3):e678–86. [PubMed: 18310188]
27. Irani DB, Berkowitz RG. Management of secondary hemorrhage following pediatric adenotonsillectomy. Int J Pediatr Otorhinolaryngol. 1997 Jun; 40(2–3):115–24. [PubMed: 9225177]
28. Ranucci M, Carlucci C, Isgrò G, Baryshnikova E. A prospective pilot study of platelet function and its relationship with postoperative bleeding in pediatric cardiac surgery. Minerva Anestesiol. 2012 May; 78(5):556–63. [PubMed: 22310193]
29. Golda T, Zerpa C, Kreisler E, Trenti L, et al. Incidence and management of anastomotic bleeding after ileocolic anastomosis. Colorectal Dis. 2013 Jan; 15(10):1301–8. [PubMed: 23710632]
30. McGinn FP, Gartell PC, Clifford PC, Brunton FJ. Staples or sutures for low colorectal anastomoses: a prospective randomized trial. Br J Surg. 1985 Aug; 72(8):603–5. [PubMed: 3896372]
31. Elhadad A. [Colorectal anastomosis: manual or mechanical? A controlled multicenter study]. Chir mémoires l'Académie Chir. 1990 Jan; 116(4–5):425–8.
32. Fingerhut A, Elhadad A, Hay JM, Lacaine F, et al. Infraperitoneal colorectal anastomosis: hand-sewn versus circular staples. A controlled clinical trial. French Associations for Surgical Research. Surgery. 1994 Sep; 116(3):484–90. [PubMed: 8079178]
33. Fingerhut A, Hay JM, Elhadad A, Lacaine F, et al. Supraperitoneal colorectal anastomosis: hand-sewn versus circular staples–a controlled clinical trial. French Associations for Surgical Research. Surgery. 1995 Sep; 118(3):479–85. [PubMed: 7652682]

34. Ciğdem MK, Onen A, Duran H, Oztürk H, et al. The mechanical complications of colostomy in infants and children: analysis of 473 cases of a single center. Pediatr Surg Int. 2006 Aug; 22(8): 671–6. [PubMed: 16838189]
35. Mollitt DL, Malangoni MA, Ballantine TV, Grosfeld JL. Colostomy complications in children. An analysis of 146 cases. Arch Surg. 1980 Apr; 115(4):455–8. [PubMed: 7362453]
36. Chandramouli B, Srinivasan K, Jagdish S, Ananthakrishnan N. Morbidity and mortality of colostomy and its closure in children. J Pediatr Surg. 2004 Apr; 39(4):596–9. [PubMed: 15065035]
37. Joint Comission and the American Medical Association-Convened Physician Consortium for Performance Improvement (PCPI). Proceedings from the National Summit on Overuse. 2012
38. Laverdière C, Gauvin F, Hébert PC, Infante-Rivard C, et al. Survey on transfusion practices of pediatric intensivists. Pediatr Crit Care Med. 2002 Oct; 3(4):335–40. [PubMed: 12780950]
39. Kris-Etherton PM. Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease. Arterioscler Thromb Vasc Biol. 2003 Feb 1; 23(2):20e–30.
40. Lawson LD, Hughes BG. Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. Biochem Biophys Res Commun. 1988 Apr; 152(1):328–35. [PubMed: 3358766]

SHORT SUMMARY

While omega-3 fatty acids are known to affect hemostatic pathways, clinical evidence supporting an increased bleeding risk is lacking. This retrospective review reports the incidence of clinically significant post-procedure bleeding in children on intravenous fish oil monotherapy for treatment of intestinal failure –associated liver disease. Findings suggest that fish oil therapy is safe, with a bleeding risk no greater than that reported in the general population.

Table 1

Subject characteristics.

Subjects	Statistic
N	183
Female sex	73 (39.9%)
Necrotizing enterocolitis diagnosis	89 (48.6%)
Age at fish oil therapy initiation (days)	89 (56, 175)
Ever on anticoagulant	19 (10.4%)
Patients with post-operative bleeding	5 (2.7%)

Table 2

Procedure characteristics.

Procedures	Statistic
N	732
Type	
Vascular access	314 (42.9%)
Abdominal	209 (28.6%)
Endoscopic	105 (14.3%)
Skin and soft tissue	50 (6.8%)
Thoracic	23 (3.1%)
Ear, nose, and throat	15 (2.1%)
Ophthalmologic	8 (1.1%)
Orthopedic	3 (0.4%)
Neurosurgical	3 (0.4%)
Other	2 (0.3%)
Age at time of procedure (months)	10.1 (5.2, 24.7)
Intravenous fish oil exposure (months)	4.6 (1.5, 13.1)
Anticoagulant prior to procedure	49 (6.7%)
Procedures complicated by CSPPB	5 (0.68%)

Abbreviations: CSPPB (clinically significant post-procedural bleeding).

Table 3

Pre- and post-operative laboratory values. Shown are median (interquartile range).

Procedures	Unknown	Statistic
Pre-operative labs		
Direct bilirubin (mg/dL)	26	0.3 (0.1, 2.4)
ALT (U/L)	22	53 (32, 101)
Albumin(g/dL)	23	3.2 (2.8, 3.7)
PTT (sec)	38	31.6 (28.4, 37.7)
ha PTT	564	32.6 (30.0, 36.5)
ha PTT (PTT if ha PTT unknown)	36	30.6 (28.1, 34.3)
INR	32	1.17 (1.08, 1.28)
Platelets ($\times 10^3$/uL)	11	244 (150, 316)
Hemoglobin (g/dL)	10	10.1 (8.8, 11.3)
Hematocrit (%)	10	30.7 (27.1, 33.9)
Total saturated FA (mmol/L)	73	2.4 (2.0, 2.9)
Total monounsaturated FA (mmol/L)	73	1.9 (1.5, 2.4)
Total polyunsaturated FA (mmol/L)	73	3.6 (2.5, 4.8)
Total ω-3 FA (mmol/L)	73	1.9 (1.3, 2.8)
Total ω-6 FA (mmol/L)	73	1.6 (1.1, 2.1)
Total ω-3:ω-6 FA	73	1.4 (1.0, 1.9)
Total FA (mmol/L)	73	8.0 (6.2, 10.0)
ARA (μmol/L)	71	377 (271, 521)
DHA (μmol/L)	72	848 (564, 1306)
EPA (μmol/L)	71	907 (592, 1243)
ALA (μmol/L)	71	37 (25, 58)
LA (μmol/L)	71	1093 (723, 1531)
T:T ratio	73	0.019 (0.014, 0.028)
EFAD	73	2 (0.3%)
Post-operative labs		
Hemoglobin (g/dL)	173	10.2 (8.8, 11.4)
Hematocrit (%)	172	30.5 (27.2, 34.5)

Abbreviations: ALT (alanine transaminase); PTT (partial thromboplastin time); haPTT (partial thromboplastin time, heparin absorbent); INR (international normalized ratio); ARA (arachidonic acid); DHA (docosahexaenoic acid); EPA (eicosapentaenoic acid); ALA (alpha-linolenic acid); LA (linoleic acid); TT (triene to tetraene); EFAD (essential fatty acid deficiency); FA (fatty acids).