The American Journal of Surgery 214 (2017) 733–737

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Risk of post-procedural bleeding in children on intravenous fish oil

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

[a] Vascular Biology Program and the Department of Surgery, Boston Children's Hospital, Boston, MA, USA
[b] Clinical Research Center, Biostatistics Core, Boston Children's Hospital, Boston, MA, USA
[c] Department of Pharmacy, Boston Children's Hospital, Boston, MA, USA
[d] Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA

ARTICLE INFO

Article history:
Received 22 August 2016
Received in revised form
19 September 2016
Accepted 31 October 2016

Keywords:
Fish oil
Omega-3 fatty acids
Intestinal failure-associated liver disease
Post-procedure bleeding

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(s) (n = 732). Five (0.68%, 95% CI 0.22–1.59%) procedures resulted in CSPPB. FO therapy was never interrupted. No deaths due to bleeding 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.

1. 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.

* Corresponding author. 300 Longwood Avenue, Fegan 3, Boston, MA, 02115, USA.
E-mail address: mark.puder@childrens.harvard.edu (M. Puder).
[e] Contributed equally to this manuscript.

http://dx.doi.org/10.1016/j.amjsurg.2016.10.026
0002-9610/

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.

2. Methods

2.1. 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 h. Exclusion criteria included patients in the database that had not undergone any type of invasive procedure while receiving intravenous FO.

2.2. 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 profile, 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.

2.3. 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.

2.4. 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).

3. 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

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%)