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Randomized Controlled Trial

Parenteral nutrition-associated cholestasis and triglyceridemia in surgical term and near-term neonates: A pilot randomized controlled trial of two mixed intravenous lipid emulsions

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SUMMARY

Background: Cholestasis is a common complication in infants receiving prolonged parenteral nutrition (PN). We studied the effects of two intravenous lipid emulsions composed with either 30% soybean oil, 30% medium-chain triglycerides (MCT), 25% olive oil, and 15% fish oil (SMOF) or with 50% MCT and 50% soybean oil n-6 (MCT/SOY) on the incidence of cholestasis in surgical term and near-term neonates.
Methods: A single-center, double-blinded, randomized controlled trial compared the incidence of cholestasis using either SMOF or MCT/SOY in neonates born at gestational age ≥34 weeks undergoing major surgery. The primary outcome was the incidence of conjugated serum bilirubin >1 mg/dL. Other liver enzymes were assessed as secondary outcomes. A post-hoc analysis assessed serum triglycerides levels. Odds ratios were estimated by mixed-effects regression models.
Results: Enrollment was prematurely interrupted because the MCT/SOY became unavailable, thus 49 infants (SMOF 22, MCT/SOY 27) completed the study. The exposure (time on PN, cumulative dose of lipids) was similar in both groups. Similar cumulative incidence rates were found for elevated conjugated bilirubinemia and other liver enzymes. Hypertriglyceridemia >250 mg/dL (12/49) was more frequent in MCT/SOY (37.0%, 95% CI 21.53–55.77) than in SMOF (9.1%, 95% CI 2.53–27.81, p = 0.024). Triglyceridemia at the first assessment (median 8 postnatal days) was significantly higher with MCT/SOY than with SMOF (181 vs. 134 mg/dL, p = 0.006). Over the whole study period, mean triglyceride concentration was 36.5 mg/dL higher with MCT/SOY compared with SMOF (p = 0.013).
Conclusion: Both emulsions had similar effects on the incidence of cholestasis and markers of liver integrity, but MCT/SOY induced higher serum triglyceride concentrations.
Trial registration: ClinicalTrials.gov, NCT02633384

1. Introduction

Intestinal failure-associated liver disease (IFALD) is a cholestatic disorder that develops in children receiving prolonged parenteral nutrition (PN) [1–3]. The etiology of IFALD in infants is multifactorial and has been linked to gut immaturity, early septic infections, and certain PN components [2–5].

Newborn infants undergoing major surgery are usually unable to receive adequate enteral nutrition for long periods of time, during which they require total and partial PN. Specific risk factors for IFALD are associated with surgery for major congenital malformations which may induce prolonged absence of enteral

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nutrition, as well as intestinal bacterial translocation [6], sepsis [4,7], and changes on enterohepatic cycle of bile acids in short bowel syndrome [6].

The use of intravenous lipid emulsions (IVLE) and their dosage have been associated with IFALD [1]. In newborn infants, phytosterol contents in some IVLE have been implicated in IFALD by inducing inflammation and antagonizing hepatic farnesoid X receptor (FXR) function in bile-acid homeostasis [1,8]. Significantly higher ratios of serum phytosterols (stigmasterol, sitosterol, and avenasterol) were found associated with direct bilirubin in infants with IFALD, compared with those without IFALD [9]. The factors associated with IFALD in patients receiving high intakes of n-6 polyunsaturated fatty acids (n-6 PUFA) with soybean oil-based IVLE are the formation of n-6 arachidonic acid, a pro-inflammatory mediator, the high provision of phytosterols, and the limited supply of alpha tocopherol relative to PUFA supply [1,8,10].

As an alternative to the soybean oil-based IVLE, newer IVLE based on mixtures of different oils provide lesser amounts of n-6 PUFA, for example a IVLE based on a 1:1 mix of medium chain triglycerides (MCT) from coconut oil and soybean oil (MCT/SOY) [11]. In children undergoing gastrointestinal surgery, PN with MCT/SOY was associated with rapid oxidation of fats for energy and more protein sparing, compared with a regimen containing exclusively SOY IVLE [12,13]. In addition, 14 days after surgery the MCT/SOY regimen was associated with lower serum levels of alanine aminotransferase (ALT), total and conjugated bilirubin [12].

In a prospective study in infants it was shown that the use of IVLE exclusively based on fish, and hence not providing appreciable amounts of phytosterols, was associated with the reversal of IFALD in infants [14]. A meta-analysis addressing the effect of fish oil-containing IVLE in neonates with IFALD requiring prolonged parenteral nutritional, suggests that these IVLE are effective for treatment but not for prevention of IFALD [15]. A mixed IVLE composed of 30% soybean oil, 30% MCT, 25% olive oil, and 15% fish oil (SMOF) was reported to protect from IFALD [16–18]. A retrospective study of 127 children aged 0–16 years, including 34 premature infants and 59 children with surgical conditions, comparing SMOF with MCT/SOY, found the use of SMOF associated with greater improvement in liver function [19].

We aimed to assess the effects of SMOF compared to MCT/SOY on the occurrence of cholestasis in term and near-term infants requiring PN after major abdominal surgery in a controlled randomized trial.

2. Material and methods

An investigator initiated, single-center, double-blinded, randomized controlled clinical trial was performed. The trial was approved by the local ethics committee and registered at ClinicalTrials.gov (NCT02633384). Written parental consent was obtained prior to study inclusion.

Eligible were neonates consecutively admitted to the neonatal intensive care unit (NICU) with a gestational age ≥34 weeks who underwent surgery for a major anomaly of the digestive tract or of a congenital anomaly affecting the digestive tract (*e.g.*, diaphragmatic hernia). Neonates were recruited within the first 48 postnatal hours, if PN (including lipids) had been initiated. Recruitment was carried out from August 2011 to February 2014. Exclusion criteria were pre-existing hepato-biliary disease, such as biliary atresia, choledochal cyst, progressive intra-hepatic familial cholestasis, infectious hepatitis, neonatal idiopathic hepatitis, biliary lithiasis, inborn errors of metabolism, and abnormalities of markers of liver function or integrity within the first 72 postnatal hours. Diagnosis of cystic fibrosis diagnosed before or after recruitment was an exclusion criterion.

Analysis was planned to be made as *per* protocol; therefore, participants were excluded from analysis if PN was required for less than 7 consecutive days, if the patient was transferred to another unit before completing 7 consecutive days of PN or if another liver related disease was diagnosed. Follow-up was interrupted whenever treatment with ursodeoxycholic acid was started (*i.e.*, the primary outcome occurred) or the IVLE was interrupted for more than 48 h for any reason, which was arbitrarily considered too long for assuming a continuous exposure.

Stratified randomization by gestational age [term (≥37 weeks) *vs.* near-term (≥34 and < 37 weeks)], was performed by one pharmacist based at the hospital pharmacy to either 20% SMOF (SMOFlipid®, Fresenius Kabi, Bad Homburg, Germany) or 20% MCT/SOY (Lipofundin®, B Braun, Melsungen, Germany) purchased by the hospital. The masked IVLE were packaged in plastic containers labeled with the patient name and infused continuously over 24 h, separately from the mixed solution of amino acids, glucose, and electrolytes. Prescribing physicians and NICU staff were unaware of the patient group assignment. The pharmacist who randomized the participants was not aware of the liver status of the participants. Both the daily and cumulative intravenous lipid intake (g/kg body weight) was recorded.

The primary outcome was the incidence of cholestasis, defined initially as conjugated bilirubin >1 mg/dL (17.1 μmol/L). After the trial initiation, the primary outcome was further specified to take into account the magnitude of total bilirubin: conjugated bilirubin >1 mg/dL (17.1 μmol/L) if total bilirubin was <5 mg/dL (85.5 μmol/L) or a conjugated bilirubin >20% of the total bilirubin if this was >5 mg/dL [20] (primary marker).

Secondary outcome was initially set as the severity of cholestasis, evaluated by the magnitude of the conjugated bilirubinemia and gamma-glutamyl transpeptidase (GGT) > 225 IU/L [21]. After the trial initiation, we also included as secondary outcome parameters total alkaline phosphatase (AP) > 608 IU/L [22]; elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), defined as >55 IU/L in female or >60 IU/L in male infants [23], were also included as markers of PN-associated liver disease.

In compliance with the PN protocol of the unit, serum levels of total and conjugated bilirubin, GGT, ALT, AST, total AP, and triglycerides were measured weekly from the first week of exposure to the interventions until discharge.

Information on the following variables was recorded: main diagnoses, date of the major surgery, reasons for reducing or stopping IVLE, day of enteral feeding initiation, type of feeding and mode of administration, percentage of daily enteral fluid intake in relation to total fluid intake (up to 50% via enteral route, and full enteral feeding), occurrence of sepsis [24] and treatment with phenobarbital or ursodeoxycholic acid.

The National Consensus for Neonatal Parenteral Nutrition was followed [25]. All participants were scheduled to receive an individualized PN within the first 24 postnatal hours, including amino acids, glucose, electrolyte and vitamins PN solution *plus* lipids (using SMOF or MCT/SOY). The glucose rate should not exceed 13 mg/kg/minute (approximately 18 g/kg/day). Heparin was added to aqueous phase of PN solution (1 IU/ml). As customized PN was not available during the weekends, infants admitted over weekends received a standard solution containing only glucose, calcium and amino acids.

Parenteral lipid intake was reduced to 0.5–1.5 g/kg/d if hypertriglyceridemia (>250 mg/dL) [2], hyperglycemia (>150 mg/dL) [2], unconjugated bilirubin >12 mg/dL [4], acute phase of sepsis [24], or

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