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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

pulmonary hypertension [4] occurred. If cholestasis was diagnosed, the parenteral intakes were limited to no more than 2–2.5 g/kg/d of lipids, 2–2.5 g/kg/d of amino acids, and 12 mg/kg/minute of glucose [2,25].

The same enteral feeding protocol was used in both groups. Minimal enteral feeding (10 ml/kg daily for five days) was initiated when bowel sounds were audibled, and significant abdominal distention and bilious or bloody gastric residuals were absent. Initially feeds were administered continuously, and changed to bolus feeding as soon as infants were considered to tolerate it. Own mother's milk was preferred if available. If sufficient amounts of own mother's milk were not available, semi-elemental or amino acid-based formulas were used as determined by the attending physician. Subsequently, these formulas were replaced by own mother's milk; if mother's milk was insufficient or unavailable either a preterm formula or an infant term formula was used.

The estimation of the sample size was based on the reported incidence of IFALD in infants, which is reported to vary from 30% to 60% [26], and on the prevalence of 20% of IFALD in this population in our NICU, from January 2010 to June 2011 (unpublished data). A sample size of 150 individuals in each group was estimated to detect a difference of 20% incidence between the two groups with 90% power, 95% confidence and 20% loss to follow-up. The recruitment period was estimated to be at least 3 years.

Categorical data are described as frequencies (percentages), and continuous variables as mean and standard deviation (SD) or median and interquartile range (25th - 75th percentiles) or minimum and maximum, as considered appropriate. Comparisons of distributions between exposure groups were performed using non-parametric tests. Incidence rates were calculated with 95% confidence intervals. Crude and adjusted odds-ratios with corresponding 95% confidence intervals were estimated using generalized linear mixed effects regression models, which take into account the correlation structure between measures over time. The level of significance $\alpha = 0.05$ was considered.

A post-hoc analysis was performed to assess the serum triglycerides levels, during the exposure to PN.

Data analysis was performed using Stata (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP., USA), and OpenEpi (Open Source Epidemiologic Statistics for Public Health. Version 2015/05/04).

3. Results

When 52 patients had been enrolled between August 2011 and December 2013 the study had to be stopped because MCT/SOY IVLE was no longer available at our hospital. No patient died. Three patients in the SMOF group were excluded because cystic fibrosis was diagnosed. The final sample includes 49 infants, 22 in the SMOF group and 27 in the MCT/SOY group. The main diagnoses of the 49 patients included in the analysis were esophageal atresia (n = 17), gastroschisis (n = 11), ileal atresia (n = 4), diaphragmatic hernia (n = 3), omphalocele (n = 2), duodenal atresia (n = 2), annular pancreas (n = 2), jejuno-ileal atresia (n = 2), meconium cyst (n = 1), persisting omphalomesenteric duct (n = 1), duodenal membrane (n = 1), congenital volvulus (n = 1), Hirschsprung disease (n = 1), and colonic atresia (n = 1). The sample characteristics are shown in Table 1. No significant differences were found in sex, gestational age, and birth weight between both groups.

Late-onset sepsis occurred in 3 patients; in two of them, the parenteral lipid intake was reduced. In 12 patients, phenobarbital was used during early postoperative period to treat drug withdrawal syndrome secondary to sedative/analgesic agents, 5 (5/22) in SMOF and 7 (7/27) in MCT/SOY (p = 1.000). No patient was treated with ursodeoxycholic acid. In 13 patients the parenteral lipid intake was temporally reduced, 5 (5/22) in SMOF group and 8 (8/27) in MCT/SOY group (p = 0.831); the causes of reduction were hypertriglyceridemia in 8 infants (4 in each group), acute phase of sepsis in 3, and temporary unavailability of central venous catheter in 2. No patient received more than 18 g/kg/day of parenteral glucose.

The weekly proportions of infants receiving exclusive PN/PN in addition to minimal enteral feeding did not differ significantly between groups throughout the study period (Table 2).

PN exposure was similar in both groups: median (min.-max.) time on PN of 16 (7–72) days, 16 days in SMOF group *vs*. 18 days in MCT/SOY group (p = 0.872); median time on exclusive PN/PN in addition to minimal enteral feeding of 8 (1–95) days, similar in both groups (p = 0.848); and median cumulative dose of intravenous lipids of 13.9 (P_{25} = 10.8, P_{75} = 18.1) g/kg (14.7 g/kg with SMOF *vs*. 12.5 g/kg with MCT/SOY, p = 0.185). Every recruited patient completed the minimum exposure requirements; therefore, no attrition occurred due to insufficient exposure to the intervention.

The occurrence of high serum levels of conjugated bilirubin, GGT, ALT, and AST did not differ significantly between the IVLE groups during the study period with respect to cumulative incidence rate, and age at diagnosis (Table 3). The serum levels of total AP remained within the normal range during the study period.

In the multivariable regression analysis (Table 4), the odds for high serum GGT increased by 2.0% for each 1 g/kg increase in cumulative dose of IVLE [adjusted OR 1.02 (95% CI 1.01–1.03); p < 0.001], without differences between groups (p = 0.562). While the odds for high serum GGT were similar whether the infants were on either exclusive PN or less than half of volume intake by enteral route (p = 0.204), the odds for high serum GGT decreased 66% when the infants received more than half of volume intake by enteral route (p = 0.008) and 85% when full enteral nutrition was achieved (p < 0.001).

As the descriptive analysis of serum triglycerides levels revealed an association with the exposure to the interventions, a post-hoc analysis was performed. Hypertriglyceridemia >250 mg/dL was diagnosed significantly more frequent with MCT/SOY than with SMOF (10 *vs*. 2 cases, p = 0.024). The cumulative incidence of hypertriglyceridemia was lower with SMOF (9.1%, 95% CI 2.53–27.81) than with MCT/SOY (37.0%, 95% CI 21.53–55.77, p = 0.024). Serum triglycerides levels were significantly higher with MCT/SOY than with SMOF (181 *vs*. 134 mg/dL; p = 0.006) at the first assessment of triglycerides (median 8 postnatal days). In

Table 1
Characteristics of the sample.

	Total N = 49	SMOF group N = 22	MCT/SOY group N = 27	p
Sex (females/males)	24/49	9/13	14/13	0.445[a]
Birth weight (g), median (P_{25}–P_{75})	2763 (2400–3105)	2678 (2331–3125)	2770 (2435–2960)	0.936[b]
Gestational age (weeks), median (P_{25}–P_{75})	38.0 (36.5–39.0)	38.5 (35.0–40.0)	37.0 (37.0–38.0)	0.404[b]

[a] Chi-square test.
[b] Mann–Whitney test.

Table 2
Proportions of infants receiving exclusive PN or PN in addition to minimal enteral feeding in relation to participants, throughout the follow-up: the weekly proportions did not differ significantly between the groups. Recruitment was carried out after completing one week of PN.

Week on PN	Total sample (nr on exclusive PN or PN in addition to MEF/nr of participants)	SMOF group (nr on exclusive PN or PN in addition to MEF/nr of participants)	MCT/SOY group (nr on exclusive PN or PN in addition to MEF/nr of participants)	p
2nd week	36/49	17/22	19/27	0.831
3rd week	9/46	3/21	6/25	0.656
4th week	5/33	2/13	3/20	1.000
5th week	2/18	1/7	1/11	1.000
6th week	1/12	1/6	0/6	1.000
7th week	1/9	1/4	0/5	0.889
8th week	1/4	1/3	0/1	1.000

MEF – minimal enteral feeding, PN – parenteral nutrition.

Table 3
Occurrence of high serum levels of conjugated bilirubin, GGT, ALT, and AST did not differ between groups (cumulative incidence rate, and age at diagnosis) during the study period (N = 49).

	High conjugated bilirubin (N = 8)			High GGT (N = 29)			High ALT (N = 8)			High AST (N = 8)		
	SMOF	MCT/SOY	p	SMOF	MCT/SOY	p	SMOF	MCT/SOY	p	SMOF	MCT/SOY	p
Nr of cases	4	4		14	15		2	6		4	4	
Cumulative incidence rate	18.2% (95% CI 2.53–27.81)	14.8% (95% CI 10.61–40.76)	0.269	63.6% (95% CI 42.95–80.27)	55.6% (95% CI 37.31–72.41)	0.567	9.1% (95% CI 2.53–27.81)	22.2% (95% CI 10.61–40.76)	0.269	16.7% (95% CI 6.68–35.85)	16.0% (95% CI 6.40–34.65)	1.000
Age at diagnosis[a]	7	9	0.234	14	15	0.186	20	23	1.000	22	30	0.486

ALT – alanine aminotransferase, AST – aspartate aminotransferase, GGT – gamma-glutamyl transpeptidase.
[a] Median postnatal days.

Table 4
Factors associated with elevated serum gama-glutamyl transpeptidase, identified by multivariable regression analysis.

Variables	OR estimates (95% CI)	p
MCT/SOY[a]	0.32 (0.01,14,98)	0.562
Lipid emulsion cumulative dose	1.02 (1.01,1.03)	<0.001
Enteral nutrition[b]		
≤50%	1.77 (1.00,3.13)	0.052
>50%	0.63 (0.28,1.41)	0.264
100%	0.15 (0.05,0.41)	<0.001

OR – odds ratio; CI – confidence interval.
[a] Reference category SMOF group.
[b] Reference category "exclusive total parenteral nutrition".

the multivariable linear regression analysis, serum triglycerides levels were significantly associated with the type of IVLE used, the cumulative dose of intravenous lipids, the duration of exclusive PN/PN in addition to minimal enteral feeding, and the proportion of enteral volume intake (Table 5): the mean serum triglyceride increase was 36.5 mg/dL higher with MCT/SOY than with SMOF (p = 0.013). Independently of the IVLE used, each increase of 1 g/kg in the cumulative dose of intravenous lipids was associated with a mean increase of 0.24 mg/dL in serum triglycerides levels (p = 0.001). Each day on exclusive PN/PN in addition to minimal enteral feeding was associated with a mean decrease of 0.92 mg/dL in serum triglycerides levels (p = 0.036); and compared with exclusive PN/PN in addition to minimal enteral feeding, enterally fed infants receiving volumes of ≤50%, >50%, or 100% of total volume supply had serum triglycerides levels (mg/dL) that were lower by 53.15, 54.89, and 73.98, respectively (p < 0.001).

Table 5
Factors associated with serum triglycerides level (mg/dL), identified by multivariable regression analysis.

Variables	β-estimate (95% CI)	p
MCT/SOY[a]	36.46 (7.85,65.06)	0.013
IV Lipid emulsion cumulative dose	0.24 (0.10,0.38)	0.001
Duration of exclusive PN/PN in addition to minimal enteral feeding (days)	−0.92 (−1.78,−0.06)	0.036
Enteral nutrition[b]		
≤50%	−53.15 (−62.33,−43.97)	<0.001
>50%	−54.89 (−68.21,−41.57)	<0.001
100%	−73.98 (−88.84,−59.13)	<0.001

CI – confidence interval; IV – intravenous; PN – parenteral nutrition.
[a] Reference category SMOF.
[b] Reference category "exclusive PN/PN in addition to minimal enteral feeding".

4. Discussion

This investigator initiated trial was prematurely stopped because one of the IVLE used became unavailable. Therefore, a smaller sample than intended of 49 neonates was included. Nonetheless, this is the largest trial to compare the safety of these two parenteral IVLE in term and near-term infants. However, the premature termination of the trial resulted in insufficient statistical power to test the primary hypothesis of a differential effect of the two IVLE on the development of cholestasis.

The exposure to the interventions, assessed by the time on PN, time on exclusive PN/PN in addition to minimal enteral nutrition, and cumulative dose of lipid intake, was similar in both randomized groups. The study was designed to be analysed as *per* protocol. Every recruited individual meeting the inclusion criteria completed the minimum exposure established in the protocol and attrition concerned only the follow-up for detection of outcomes; therefore, the analysis ended up as if it had been by intention to treat.

To evaluate an association of early stages of cholestasis with IVLE administration, the cut-off >1 mg/dL for conjugated bilirubin [20] was used, although a cut-off >2 mg/dL is mostly used in clinical practice for defining IFALD [27]. The cumulative incidence rates of elevated serum conjugated bilirubin, GGT, AST, and ALT were similar in both groups, although a trend to a greater incidence of high ALT in the MCT/SOY group was noticed. No cases of high serum total AP were detected. In a systematic review on the use of IVLE with fish oil in children with intestinal failure, significant differences favoring IVLE with fish oil over those without were found for

ALT, despite the very low magnitude of differences [28]. The absence of detectable differences in liver enzyme levels in our trial might be due to the premature completion of the trial precluding sufficient statistical power to test this question. Moreover, in approximately one quarter of infants phenobarbital was used in the early postoperative period for treatment of drug withdrawal syndrome secondary to sedative/analgesic agents. Phenobarbital might have reduced the incidence of IFALD through its choleretic effect, although no firm evidence on this effect has been established in neonates [29].

The odds for high serum GGT increased significantly with the cumulative dose of IVLE, independently of the IVLE used. The association of cumulative dose of intravenous IVLE with high serum GGT levels but not with other serum markers of IFALD may be related to early stages of hepatic damage induced by IVLE or merely reflect a strong protective effect of enteral feeding, because the cumulative IVLE dose was inversely related to the amount of enteral feeds provided.

In a retrospective study, including premature infants and older children, using SMOF was associated with less alteration of hepatic function than the use of MCT/SOY [19]. In our trial with the same IVLE, we had intended to assess efficacy of prevention of cholestasis associated to PN in a more homogeneous population of term and near-term infants.

While we cannot answer this primary question, we found hypertriglyceridemia significantly more frequent in infants receiving MCT/SOY than SMOF. At 8 postnatal days, when most infants received exclusive PN and only a few had started minimal enteral feeding, serum triglycerides were significantly higher in the MCT/SOY group. A *post-hoc* multivariable analysis was performed to better address the plasma clearance of serum triglycerides. Infants receiving MCT/SOY had a significantly greater mean increase in the serum triglyceride levels during the study. Independently of the IVLE used, the cumulative dose of intravenous lipids was found to induce a modest but significant increase of triglyceride levels, while the proportion of total enteral volume intake decreased significantly the serum triglyceride levels. Unexpectedly, a longer time period of exclusive PN after birth was associated with a small but statistically significant decrease in triglyceride levels. In clinical practice, triglyceride levels are often used to monitor the clearance and metabolic tolerance of IVLE [30]. Some factors potentially affecting serum triglycerides levels in infants [30] were similar in both arms of the trial, such as the IVLE dosage, the packaging in plastic containers, the concentration of heparin added to PN solutions, and the 24-h continuous infusion of IVLE. Other factors that may affect the bloodstream clearance of intravenous triglycerides entail enzymatic and nonenzymatic pathways [31,32], diameter of triglyceride droplets of IVLE [33], and the type of triglyceride substrate, i.e., chain length distribution of fatty acids, degree of fatty acid unsaturation and double bond position, and the positional distribution of specific fatty acids within the triacylglyceride molecule [34,35]. In a cohort study, serum triglyceride levels declined more rapidly over time in children receiving fish-oil based IVLE than in those receiving soy-oil based IVLE [14]. The pathways responsible for the clearance of intravenously infused MCT, n-3 fatty acid-rich fish oil, and n-6 fatty acid-rich soybean oil differ considerably [31,32]. MCT are good substrates for lipoprotein lipase-mediated hydrolysis [36], while fish oil-based triglycerides, rich in long-chain n-3 PUFAs, are poor substrates when their proportions exceed 20% triglycerides [37]. The inclusion of MCT in mixed IVLE appears to compensate for the slow hydrolysis of fish oil-based triglycerides, and the concomitant presence of both n-3 PUFA-rich triglycerides and MCT may facilitate tissue uptake of remnant particles [31,38]. Moreover, SMOF was shown to have higher droplet size compared with a IVLE composed of 50% MCT, 40% soybean oil and 10% fish oil, even though both IVLE met the pharmacopeial specifications [39]. In animal models, addition of fish oil triglycerides to IVLE was found to increase blood clearance of large size emulsion particles, probably due to increased particle uptake by extra-hepatic tissues [40,41]. In adults with hypertriglyceridemia, fish oils were effective in reducing triacylglycerol and particularly VLDL triacylglycerol levels [42]. Finally, the influence of the type of IVLE container on fat globule size is controversial. In critically ill neonates receiving the same intravenous IVLE, a higher incidence of hypertriglyceridemia was associated to poor clearance of large-diameter fat globules when the IVLE was packaged in plastic containers compared with glass containers [43]. In another study, IVLE either in glass or plastic containers exhibited identical time dependent behavior with respect to mean globule size [44]. In our hospital, only plastic containers are used for IVLE. Although SMOF contains long-chain n-3 fatty acids and has lower proportion of MCT in comparison with MCT/SOY, we lowered serum triglycerides using SMOF rather than MCT/SOY. Since SMOF is a complex mixture composed of molecules with different metabolic properties potentially affecting plasma triglycerides clearance, further investigation is needed to explore the pathways and components of SMOF that could explain such differences in infants.

Statement of authorship

LPdS: designed the research, draft the manuscript, and has final responsibility for its content; SN: participated in the data collection; MLR: responsible for preparation of parenteral nutrition and randomized; MA: contributed with the statistical analyses; AP: participated in the data collection; DV: designed the clinical trial, analyzed the data and contributed to draft the manuscript; ALP: conceived the sampling method and data analysis; MS: critically review the manuscript; GCF: critically review the manuscript; BK: contributed to data interpretation and critically reviewed and contributed to the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

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