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ORIGINAL RESEARCH

Association between mixed fatty acid emulsion and parenteral nutrition–associated cholestasis in extremely low-birth-weight infants: A retrospective cohort study

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Abstract

Background: Soybean oil lipid emulsions have been implicated in the development of parenteral nutrition–associated cholestasis (PNAC) in premature infants. A recent mixed fatty acid emulsion containing soybean oil, medium-chain triglycerides (MCTs), olive oil, and fish oil may reduce the incidence of PNAC, but evidence remains conflicting. The aim of this study was to evaluate the effect of mixed fatty acid emulsion on PNAC in extremely low-birth-weight (ELBW) infants.

Methods: We performed a retrospective cohort study on ELBW infants from 2016 to 2022. ELBW infants who received MCT/long-chain triglyceride (LCT) lipid emulsion or mixed fatty acid emulsion were compared. The primary outcome was the incidence of PNAC. Secondary outcomes included peak levels of direct bilirubin and bronchopulmonary dysplasia. Multivariable analysis was performed to adjust for potential confounders.

Results: A total of 180 ELBW infants were reviewed in this study. Twenty-six of 99 patients (26.2%) in the mixed fatty acid emulsion group and 29 of 81 patients (35.8%) in the MCT/LCT lipid emulsion group developed PNAC ($P = 0.17$). There was no significant difference in median peak direct bilirubin and the rate of bronchopulmonary dysplasia. The results remained consistent after adjusting for potential confounders. Time to PNAC, rate of rise of direct bilirubin, and age of direct bilirubin normalization were not statistically different between groups.

Conclusions: Compared with MCT/LCT lipid emulsion, mixed fatty acid emulsion did not reduce the incidence or degree of PNAC in ELBW infants.

KEYWORDS
cholestasis, extremely low birth weight infants, lipid emulsion, parenteral nutrition, premature

INTRODUCTION

In recent years, with the progress of obstetrical management and neonatal intensive care, the survival rate of premature infants, especially extremely preterm and extremely low-birth-weight (ELBW) infants, has been improved.[1,2] Parenteral nutrition is crucial for the growth and development of preterm infants who were unable to reach full enteral feeds shortly after birth owing to gastrointestinal immaturity and incoordination of sucking, swallowing, and breathing. Moreover, ELBW infants may require long-duration parenteral nutrition because of the high incidence of sepsis, feeding intolerance, and necrotizing enterocolitis, etc. Although the provision of parenteral nutrition supplied adequate energy and nutrients to premature neonates, several complications have arisen. Parenteral nutrition–associated cholestasis (PNAC), also known as parenteral nutrition–associated liver disease or intestinal failure–associated liver disease in some literature, is one of the most severe morbidities related to long-term parenteral nutrition, which can progress to cirrhosis, portal hypertension, and end-stage liver disease requiring liver transplant or even leading to death.[3–5]

Although the etiology of PNAC is multifactorial, with risk factors including preterm birth, low birth weight, sepsis, necrotizing enterocolitis, lack of enteral feeding, and specific components of parenteral nutrition, soybean oil–based lipid emulsions were considered to play a significant role in the pathogenesis of PNAC. The potential mechanisms include inflammatory response and oxidative stress due to ω-6 long-chain polyunsaturated fatty acids, as well as toxic effects from phytosterols and a lack of alpha-tocopherol.[6] In view of this concern, alternative formulations have been explored. A mixed fatty acid emulsion containing soybean oil, medium-chain triglycerides (MCTs), olive oil, and fish oil (SMOF) is theoretically beneficial to prevent PNAC because of its more balanced fatty acids profile. This formulation differs fundamentally from traditional MCT/long-chain triglyceride (LCT) emulsions through reduced soybean oil content, thereby limiting exposure to both ω-6 long-chain polyunsaturated fatty acids and phytosterols. The olive oil component provides ω-9 monounsaturated fatty acids that are less susceptible to lipid peroxidation.[7] Fish oil, a key component of SMOF lipid emulsion, has a high content of ω-3 long-chain polyunsaturated fatty acids, such as docosahexaenoic acid and eicosapentaenoic acid, which are associated with anti-inflammatory properties. Notably, clinical studies have reported that fish oil can reverse PNAC,[8–12] and animal studies suggest that fish oil can alleviate parenteral nutrition–associated liver disease and intestinal injury by regulating the homeostasis of bile acid enterohepatic circulation and altering microbiota composition in different intestinal segments.[13] Additionally, SMOF lipid is supplemented with alpha-tocopherol, a potent antioxidant at approximately 200 mg/L.

Multiple studies suggested that SMOF lipid emulsion can reduce the incidence of PNAC compared with conventional soybean oil–based lipid emulsion.[14–20] However, the efficacy of SMOF lipid emulsion in preventing PNAC remains controversial, as some studies report no significant benefits.[21–23] Furthermore, data in ELBW infants are particularly limited. In this study, we hypothesized that SMOF lipid injectable emulsion is associated with decrease in PNAC compared with MCT/LCT lipid injectable emulsion in ELBW infants. Using a retrospective cohort design, we aimed to provide new evidence on the comparative effectiveness of these lipid emulsions in preventing PNAC, thereby informing clinical practice and future research.

METHODS

We performed a single-center retrospective cohort study on 180 ELBW infants (birth weight < 1000 g) admitted to a neonatal intensive care unit from January 2016 to December 2022. Our exposure of interest was SMOF lipid injectable emulsion (SMOFlipid, Fresenius Kabi) composed of 30% soybean oil, 30% MCTs, 25% olive oil, and 15% fish oil. And our comparator was MCT/LCT lipid injectable emulsion (Lipofundin MCT/LCT 20%, B. Braun) composed of 50% soybean oil and 50% coconut oil. Our primary outcome was PNAC defined as direct bilirubin levels >2 mg/dl while receiving parenteral nutrition for >14 days.[6] Infants with other identifiable causes of cholestasis (eg, infection with cytomegalovirus or hepatitis virus, hemolysis, congenital biliary atresia, inborn errors of metabolism) were not considered to have PNAC. Our secondary outcomes were peak levels of direct bilirubin and bronchopulmonary dysplasia. Multivariable binary logistic regression analysis was performed to adjust for potential confounders, including sex, gestational age, birth weight, necrotizing enterocolitis, sepsis, and duration of parenteral nutrition. The present study was reviewed and approved by the ethics committee of the Children's Hospital of Zhejiang University School of Medicine. ELBW infants who were admitted before 72 h of life and received parenteral nutrition for at least 14 days were included. Based on prior experience at our institution, we expected the incidence of PNAC among ELBW infants to be approximately 40%. The sample size was calculated based on an expected disease incidence of 40% in the control group and a 50% reduction in the primary outcome with a type I error of 5% and power of 80%; a total of 158 participants (79 per group) were required. To ensure robust confounder adjustment and account for potential missing data while minimizing selection bias, we included all eligible infants from 2016 to 2022 (final $n = 180$), a period with standardized nutrition practices. In the first period, from January 2016 to June 2018, all ELBW infants received MCT/LCT lipid injectable emulsion as parenteral nutrition. During the second period, from July 2018 to December 2022, all infants given parenteral nutrition received SMOF lipid injectable emulsion. The compositions of SMOF lipid injectable emulsion and MCT/LCT lipid emulsion are shown in Table S1. We retrospectively reviewed the clinical data of patients by searching the electronic medical record system. Baseline demographic characteristics, parenteral nutrition data, morbidities, and mortality of each group were compared.

Nutrition strategy

The nutrition strategy at our neonatal intensive care unit follows the recommendations of Chinese Clinical Guidelines for Neonatal

Nutritional Support.[24] Nutrition management remained consistent throughout the study period, with the exception of the introduction of donated breast milk in January 2021. Parenteral nutrition was initiated on the day of admission. Regardless of whether participants were in the MCT/LCT lipid emulsion or SMOF lipid emulsion group, intravenous lipid emulsions were administered at a dose of 0.5–1 g/kg/day and were gradually increased by 0.5 g/kg/day up to a maximum of 3–4 g/kg/day. The dosage of lipid emulsions was reduced or halted if serum triglyceride concentrations during infusion exceed 3 mmol/L (265 mg/dl). Glucose was typically initiated at 4–6 mg/kg/min and was titrated up to 12–14 mg/kg/min. All eligible ELBW infants received amino acids with a dose of 3–4 g/kg/day. Enteral feedings were initiated as soon as possible with either breast milk or premature formula. Enteral nutrition was started at 10 ml/kg/day and advanced by 10–20 ml/kg/day if feeding tolerance was achieved. After reaching volumes of 50–100 ml/kg/day, breast milk was fortified. Parenteral nutrition was stopped when enteral feeds reached 140–160 ml/kg/day. Reduction of lipid emulsions to 1 g/kg/day dose was performed and ursodeoxycholic acid was administered when ELBW infants developed PNAC. Infants received fish oil (Omegaven; Fresenius Kabi) as rescue therapy with a dose of 1 g/kg/day if direct bilirubin was >5 mg/dl.

Definitions

PNAC was defined as direct bilirubin levels >2 mg/dl while receiving parenteral nutrition >14 days, and infants with other identifiable causes of cholestasis (eg, infection with cytomegalovirus or hepatitis virus, hemolysis, congenital biliary atresia, inborn errors of metabolism) were excluded. Blood biochemical examinations were performed every 1–2 weeks on average. Small for gestational age was defined as birth weight in the <10th percentile for the gestational age according to Fenton growth charts.[25] Sepsis was defined as the presence of clinical signs of infection (eg, temperature instability, respiratory distress, or hemodynamic instability), elevated inflammatory marker concentrations (eg, C-reactive protein or procalcitonin), and a blood culture positive for infection. Necrotizing enterocolitis was diagnosed according to modified Bell's criteria (stage ≥IIa).[26] Bronchopulmonary dysplasia was defined as positive-pressure ventilation or oxygen dependency at 36 weeks' postmenstrual age or at discharge, or death before 36 weeks.[27,28] The screening for retinopathy of prematurity was performed by ophthalmologist starting at 4–6 weeks of age. The extent and severity of retinopathy of prematurity was described according to the International Classification of Retinopathy of Prematurity,[29] and treatment (laser or intravitreal ranibizumab) was initiated when the infants developed high-risk prethreshold retinopathy of prematurity, also called "type 1 retinopathy of prematurity," as follows: any stage retinopathy of prematurity with plus disease in zone I; stage 3 retinopathy of prematurity without plus disease in zone I; stage 2 or 3 retinopathy of prematurity with plus disease in zone II.[30,31] Hemodynamically significant patent ductus arteriosus was treated with medications (indomethacin/ibuprofen) or surgical ligation if necessary based on clinical manifestations and echocardiographic findings.[32,33] We diagnosed intraventricular hemorrhage and periventricular leukomalacia by cerebral ultrasound, computed tomography, or magnetic resonance imaging. The Papile criteria were used to evaluate intraventricular hemorrhage.[34]

Statistical analysis

Normally distributed data were presented as mean (SD) and assessed by Student *t* test; continuous data of nonnormal distribution were expressed as median (IQR) and analyzed by the rank sum test. Categorical data were presented as frequency (percentage) and compared by chi-square test or Fisher exact test as appropriate. All statistical analyses were undertaken using IBM SPSS Statistics 26.0 software. Significance testing was performed with the use of a two-sided alpha level of 0.05.

RESULTS

A total of 180 ELBW infants were included in this study, with 99 receiving SMOF lipid emulsion and 81 receiving MCT/LCT lipid emulsion. The two groups were similar in baseline demographic and clinical characteristics with no significant differences, although the birth weights in the group receiving SMOF lipid emulsion were slightly lower (Table 1). As shown in Table 2, there were no statistical differences in terms of nutrition parameters between groups. The mean duration of parenteral nutrition, mean duration of lipid emulsions, lipid intakes, protein intakes, and onset of enteral nutrition were comparable in both groups. The mean actual parenteral nutrition energy intakes did not differ between groups (71.3 vs 73.1 kcal/kg/day, $P = 0.13$). No significant differences were observed in enteral nutrition volume or energy between the SMOF lipid emulsion and MCT/LCT lipid emulsion groups during the first 14 days of life. The two groups were also similar in the incidence of rescue therapy with fish oil.

Primary and secondary outcomes are presented in Table 3. The incidence of PNAC in the SMOF lipid emulsion group was lower than MCT/LCT lipid emulsion group, but this did not reach statistical significance (26.2% vs 35.8%, $P = 0.17$). After adjusting for potential confounders, including sex, gestational age, birth weight, necrotizing enterocolitis, sepsis, and duration of parenteral nutrition, the incidence of PNAC remained comparable between the two groups. There was no significant difference in median peak direct bilirubin of infants with PNAC (56.1 vs 68.5 μmol/L, $P = 0.57$) between SMOF lipid emulsion and MCT/LCT lipid emulsion groups. The incidence of bronchopulmonary dysplasia was comparable between the SMOF lipid emulsion and MCT/LCT lipid emulsion groups (45.4% vs 48.1%, $P = 0.72$). Changes in direct bilirubin were similar between the SMOF lipid emulsion and MCT/LCT lipid

TABLE 1 Demographic and clinical characteristics at baseline.

Characteristics	SMOF (*N* = 99)	MCT/LCT (*N* = 81)	*P**
Sex (M/F), *N*	48/51	48/33	0.15
Gestational age, median (IQR), weeks	27.1 (26–29)	27.4 (26.4–29.8)	0.09
Birth weight, median (IQR), g	860 (770–930)	890 (840–950)	0.06
Birth weight *Z* score, median (IQR)	−0.5 (−1.2 to 0.1)	−0.5 (−1.5 to 0)	0.46
Cesarean delivery, *N* (%)	47 (47.5)	40 (49.4)	0.51
Multiple pregnancy, *N* (%)	45 (45.5)	36 (44.4)	0.89
SGA, *N* (%)	21 (21.2)	22 (27.2)	0.35
PROM, *N* (%)	26 (26.3)	22 (27.2)	0.89
1-min Apgar, median (IQR)	8 (5–9)	8 (5–9)	0.51
5-min Apgar, median (IQR)	9 (8–10)	9 (8–10)	0.58
Antenatal steroids, *N* (%)	27 (27.3)	16 (19.8)	0.24
Surfactant, *N* (%)	67 (67.7)	49 (60.5)	0.32
Death, *N* (%)	5 (5.1)	5 (6.2)	0.74
Length of stay, mean (SD), days	81 (28.1)	78.2 (22.2)	0.47
Hypertriglyceridemia, *N* (%)	23 (23.2)	17 (21)	0.61
Sepsis, *N* (%)	22 (22.2)	26 (32.1)	0.14
NEC ≥IIa, *N* (%)	9 (9.1)	4 (4.9)	0.28
Abdominal surgery, *N* (%)	14 (14.1)	8 (9.9)	0.39
Intervention for ROP, *N* (%)	19 (19.2)	15 (18.5)	0.91
PDA requiring treatment, *N* (%)	50 (50.5)	34 (42)	0.25
IVH (III–IV), *N* (%)	7 (7.1)	3 (3.7)	0.33
PVL, *N* (%)	4 (4.0)	3 (3.7)	0.91

Abbreviations: IVH, intraventricular hemorrhage; LCT, long-chain triglyceride; M/F, male/female; MCT, medium-chain triglyceride; NEC, necrotizing enterocolitis; PDA, patent ductus arteriosus; PROM, premature rupture of membrane; PVL, periventricular leukomalacia, ROP, retinopathy of prematurity; SGA, small for gestational age; SMOF, soybean oil, medium-chain triglycerides, olive oil, and fish oil.

*Groups were compared using a Student *t* test or rank sum test for continuous variables and chi-square or Fisher exact test for categorical variables.

emulsion groups (presented in Table 4). Time to PNAC, rate of rise of direct bilirubin, and age of direct bilirubin normalization were not statistically different between groups. Peak levels of alanine transaminase, aspartate transaminase, and alkaline phosphatase did not differ significantly. Peak levels of glutamyltransferase were significantly lower in SMOF lipid emulsion group compared with MCT/LCT lipid emulsion (145 vs 194 U/L, $P = 0.001$).

Subgroup analysis of infants who required parenteral nutrition for >28 days and those with necrotizing enterocolitis stage II+ was performed (Table 5). Among infants requiring parenteral nutrition for >28 days, the PNAC incidence remained numerically lower in the SMOF lipid emulsion group (30.2% vs 38.1%), although this difference did not reach statistical significance ($P = 0.29$). In the necrotizing enterocolitis stage II+ subgroup ($n = 13$), PNAC occurred in four of nine (44.4%) infants exposed to SMOF lipid emulsion vs two of four (50.0%) controls ($P = 1.0$, Fisher exact test).

DISCUSSION

In the present study, we compared the incidence and degree of PNAC between ELBW infants receiving either SMOF lipid injectable emulsion or MCT/LCT lipid injectable emulsion as the initial lipid strategy, and the recovery of cholestasis was also followed up. There was no significant difference in the incidence of PNAC (26.2% vs 35.8%, $P = 0.17$) and median peak direct bilirubin of infants with PNAC (56.1 vs 68.5 μmol/L, $P = 0.57$) between SMOF lipid emulsion and MCT/LCT lipid emulsion groups. The results remained consistent after adjusting for potential confounders, including sex, gestational age, birth weight, necrotizing enterocolitis, sepsis, and duration of parenteral nutrition. Rate of rise of direct bilirubin, time to PNAC, and age of direct bilirubin normalization were also not statistically different between groups. Belza et al demonstrated that neonates with intestinal failure receiving SMOF lipid emulsion had a lower incidence and decreased severity of PNAC over the first 12 months of

TABLE 2 Nutrition parameter.

Variable	SMOF (*N* = 99)	MCT/LCT (*N* = 81)	*P**
Duration of PN, mean (SD), days	50.7 (21)	52.4 (17.3)	0.56
Duration of LE, mean (SD), days	47.7 (20.3)	47.3 (16.0)	0.89
Onset of EN, median (IQR), days	2 (1–3)	2 (1–3)	0.61
Average lipid intake, mean (SD), g/kg/days	2.3 (0.3)	2.3 (0.3)	0.86
Actual lipid intake, median (IQR), g	120 (76.5–160)	134 (84.9–180.5)	0.18
Average protein intake, mean (SD), g/kg/days	2.5 (0.4)	2.5 (0.3)	0.92
Actual protein intake, mean (SD), g	155 (79.1)	176 (76.1)	0.07
Actual PN energy intake, mean (SD), kcal/kg/days	71.3 (8.7)	73.1 (6.9)	0.13
Enteral intake within the first 14 days, median (IQR), ml/kg/days	16 (7–31)	14 (6–24.8)	0.38
Actual enteral energy within the first 14 days, median (IQR), kcal/kg/days	11 (5.5–20.6)	10 (4.2–16.8)	0.42
Rescue therapy, *N* (%)	10 (10.1)	11 (13.6)	0.47
Weight at discharge, median (IQR), g	2565 (2247–2950)	2750 (2355–3217)	0.10
Weight at discharge *z* score, median (IQR)	−1.7 (−2.3 to −0.7)	−1.3 (−2.4 to −0.5)	0.62
Δ*z* Score of weight, mean (SD)	−1.0 (0.8)	−0.8 (0.8)	0.07

Abbreviations: EN, enteral nutrition; LCT, long-chain triglyceride; LE, lipid emulsion; MCT, medium-chain triglyceride; PN, parenteral nutrition; SMOF, soybean oil, medium-chain triglycerides, olive oil, and fish oil.

*Groups were compared using a Student *t* test or rank sum test for continuous variables and chi-square or Fisher exact test for categorical variables.

TABLE 3 Primary and secondary outcomes.

Outcome	SMOF (*N* = 99)	MCT/LCT (*N* = 81)	*P**	*P′*
Primary outcome				
PNAC, *N* (%)	26 (26.2)	29 (35.8)	0.17	0.77
Secondary outcome				
Peak DBIL, median (IQR), μmol/L	56.1 (47–121.1)	68.5 (50.9–119.5)	0.57	0.39
BPD, *N* (%)	45 (45.4)	39 (48.1)	0.72	0.99

Abbreviations: BPD, bronchopulmonary dysplasia; DBIL, direct bilirubin; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; PNAC, parenteral nutrition–associated cholestasis; SMOF, soybean oil, medium-chain triglycerides, olive oil, and fish oil.

*Groups were compared using a Student *t* test or rank sum test for continuous variables and chi-square or Fisher exact test for categorical variables. *P′* represents adjusted *P* values from multivariable binary logistic regression analysis, controlling for sex, gestational age, birth weight, necrotizing enterocolitis, sepsis, and duration of parenteral nutrition.

treatment compared with those receiving traditional soybean-based lipid emulsions.[14] In a separate study of infants with intestinal failure receiving SMOF lipid emulsion or Intralipid (Fresenius Kabi) during the first 8 weeks of parenteral nutrition, the authors did not find a significant difference in incidence or degree of cholestasis, but those receiving SMOF lipid emulsion resolved their cholestasis more quickly compared with the group receiving Intralipid.[15] Additionally, a pilot randomized controlled trial showed that SMOF lipid emulsion can reduce the risk of progressive PNAC in children with intestinal failure, and patients receiving SMOF lipid emulsion were also more likely to have a decrease in serum conjugated bilirubin to 0 μmol/L than those in the Intralipid group.[16] However, the participants in these studies were patients with intestinal failure, which is different from our research. Although we performed prespecified subgroup analyses for high-risk populations (infants requiring parenteral nutrition >28 days and those with necrotizing enterocolitis stage II+), no statistically significant differences in PNAC incidence were observed between treatment groups in either subgroup. This finding may be attributed to the relatively low number of surgically managed cases (eg, infants with enterostomies) in our cohort and the small subgroup sample sizes, particularly in the necrotizing enterocolitis subgroup (*n* = 13).

In a retrospective study by Jackson et al, 136 neonates who received either SMOF lipid emulsion or Intralipid emulsions were compared. Nine of 55 patients (16.4%) in the Intralipid emulsion group and 2 of 81 patients (2.5%) in the SMOF lipid emulsion group

TABLE 4 Changes in DBIL levels and liver enzyme levels between two groups.

Variable	SMOF (*N* = 99)	MCT/LCT (*N* = 81)	*P**
Time to PNAC, mean (SD), days	42.3 (19.2)	44.7 (18.0)	0.64
Time to peak DBIL, median (IQR), days	67.5 (45.8–90.5)	67 (52.5–81.5)	0.94
Rate of rise of DBIL, median (IQR), μmol/L/week	7.2 (4.7–10.6)	6.9 (4.1–11.7)	0.75
Age of DBIL normalized, median (IQR), days	101 (63.5–131.5)	106 (92–133)	0.29
ALT, median (IQR), U/L	17 (12–44)	21 (12–48)	0.54
AST, median (IQR), U/L	64 (43–111)	69 (53–153)	0.13
Gamma-GT, median (IQR), U/L	145 (93–212)	194 (141.5–285)	0.001
ALP, mean (SD), U/L	585 (199)	631 (215)	0.14

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; DBIL, direct bilirubin; GT, glutamyltransferase; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; PNAC, parenteral nutrition–associated cholestasis; SMOF, soybean oil, medium-chain triglycerides, olive oil, and fish oil.

*Groups were compared using a Student *t* test or rank sum test for continuous variables.

TABLE 5 Subgroup analyses of PNAC incidence.

Subgroup	SMOF group PNAC, % (*n*/*N*)	MCT/LCT group PNAC, % (*n*/*N*)	*P**
PN > 28 days	30.2 (26/86)	38.1 (29/76)	0.29
NEC stage II+	44.4 (4/9)	50.0 (2/4)	1.0

Abbreviations: NEC, necrotizing enterocolitis; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; PNAC, parenteral nutrition–associated cholestasis; SMOF, soybean oil, medium-chain triglycerides, olive oil, and fish oil.

*Groups were compared using chi-square or Fisher exact test for categorical variables.

had developed cholestasis ($P = 0.007$) at or before 30 days after parenteral nutrition initiation.[17] On the contrary, another study of 215 premature neonates found that mixed oil lipid emulsion was not associated with a lower risk of cholestasis.[35] Similarly, Ferguson's study showed that duration of parenteral nutrition and duration of lipids were significant risk factors for development of PNAC regardless of type of lipid emulsion when comparing the incidence and severity of PNAC in a highly surgical neonatal population receiving SMOF lipid emulsion or Intralipid emulsion for long-term parenteral nutrition.[23] Choudhary et al compared clinically outcomes in preterm infants aged <32 weeks receiving Intralipid vs SMOF lipid emulsion, yet no significant difference was noted in rates of PNAC.[22] A recent Cochrane meta-analysis in preterm infants found no evidence of a difference in the incidence of PNAC between fish oil lipid and non–fish oil lipid emulsions.[36] Repa et al conducted a randomized controlled trial to examine whether a mixed lipid emulsion reduces the incidence of PNAC in ELBW infants.[21] Similar to our results, they showed that the incidence of PNAC was not significantly reduced using a mixed lipid emulsion. We noticed that most literature has compared clinical outcomes of SMOF lipid emulsion with Intralipid, but not with MCT/LCT lipid emulsion, which may have potential benefits in reducing cholestasis. Kasirer et al compared the incidence and severity of direct hyperbilirubinemia in very low-birth-weight infants and suggested that SMOF lipid emulsion group had a lower incidence of PNAC ($P = 0.022$) and lower peak direct bilirubin levels ($P = 0.018$) compared with the MCT/LCT lipid emulsion group.[19] However, gestational age and birth weight of the SMOF lipid emulsion group were higher than those of the MCT/LCT lipid emulsion group (28.9 vs 27.7 weeks and 1290 vs 890 g, respectively).

The observed results may reflect the composition of SMOF lipid emulsion, which contains 15% fish oil and 30% soybean oil. Although the fish oil component provides anti-inflammatory and hepatoprotective benefits, its relatively low proportion may not fully counteract the proinflammatory effects of soybean oil. This imbalance could explain the lack of significant differences in PNAC incidence between the SMOF lipid emulsion and MCT/LCT lipid emulsion groups. Currently, pure fish oil emulsions, such as Omegaven, are primarily used for the rescue therapy cholestasis rather than for routine parenteral nutrition.[37] A double-blind randomized controlled trial by Nehra et al compared pure fish oil with pure soybean oil in preventing PNAC.[38] But the incidence of cholestasis among enrolled patients was significantly lower than expected, resulting in early study termination and an inability to assess for differences in the incidence of cholestasis. Future studies should explore the effects of higher fish oil content or alternative lipid formulations on PNAC in ELBW infants.

Our study found that the use of SMOF lipid emulsion did not significantly reduce the incidence of bronchopulmonary dysplasia in ELBW infants compared with MCT/LCT lipid emulsion. Currently, whether lipid emulsion could affect the incidence of bronchopulmonary dysplasia in preterm infants was still in controversy. A recent randomized controlled trial revealed that lipid emulsions containing fish oil can attenuate inflammatory cytokines and the development of bronchopulmonary dysplasia in very premature infants.[39] Asfour et al reported that preterm infants who received SMOF lipid emulsion as part of their parenteral nutrition in their early life have a lower bronchopulmonary dysplasia rate when

compared with those received Intralipid.[40] However, a systematic review and meta-analysis of 3781 infants in 22 included studies showed that fish oil–containing lipid emulsions have no protective effect against the occurrence of bronchopulmonary dysplasia in preterm infants.[41] Similar findings were reported in the study by Repa et al; they found no difference in bronchopulmonary dysplasia when using SMOF lipid emulsion compared with soybean oil–based lipid emulsion in ELBW infants.[21]

Several studies suggested that SMOF lipid emulsion may improve the neurodevelopmental outcomes of preterm infants.[42–44] In present study, we failed to find significant differences in the incidence of intraventricular hemorrhage and periventricular leukomalacia between groups, but the long-term neurodevelopmental outcomes were not discussed in this study. The limitations of our study need to be acknowledged. Firstly, this is a retrospective study performed in two different periods, and subtle changes in practice may influence outcomes. As a retrospective study, it is subject to potential biases, including selection bias and unmeasured confounding factors, despite our efforts to adjust for known confounders. Second, the sample size, although adequate for the primary analysis, may have limited the power to detect smaller differences in secondary outcomes or subgroup analyses. For example, the small number of infants with necrotizing enterocolitis precluded meaningful subgroup analysis in this population. Third, the single-center design may limit the generalizability of our findings to other settings with different patient populations or clinical practices. The prolonged parenteral nutrition duration in our cohort reflects both the high-acuity nature of our regional referral population and conservative feeding practices during the study period. Although this enhances the generalizability to complex ELBW infants cases, it may limit direct comparison with centers that use more aggressive enteral feeding protocols.

CONCLUSIONS

The results of this study demonstrated that mixed fatty acid emulsion did not decrease the incidence or degree of PNAC compared with MCT/LCT lipid emulsion in ELBW infants. Large randomized controlled trials are warranted.

AUTHOR CONTRIBUTIONS

Tian Xie: Conceptualization; methodology; writing—original draft. **Hongfang Mei**: Methodology; software; formal analysis. **Mingyan Chen**: Methodology; validation; investigation. **Yanping Xu**: Data curation; supervision; writing—review and editing. **Xiaolu Ma**: Conceptualization; investigation; supervision; project administration. **Liping Shi**: Conceptualization; methodology; writing—review and editing. **Zheng Chen:** Conceptualization; writing—original draft; project administration.

CONFLICT OF INTEREST STATEMENT

None declared.

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