Original Article

Very low birth weight preterm infant complications where parenteral nutrition is soy or fish oil-based: A retrospective study in Shanghai

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Background and Objectives: To examine whether a parenteral mixed lipid emulsion containing fish oil reduces the incidence of cholestasis, retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) in very low birth weight (VLBW, birth weight <1500 g) infants. **Methods and Study Design:** This retrospective study was conducted in the neonatal intensive care unit of the Children's Hospital of Fudan University. Patients received either a soybean and medium-chain oil (MCT)-based lipid emulsion (Lipofundin) or a mixed lipid emulsion consisting of soybean oil, medium-chain triglycerides, olive oil, and fish oil (SMOF) as parenteral nutrition. The primary outcomes were cholestasis, ROP and BPD, and the secondary outcomes were necrotizing enterocolitis (NEC) and sepsis. **Results:** A total of 149 premature infants (78 in the soybean oil group and 71 in the fish oil group) were included in this study. Multivariate logistic regression analysis showed that gestational age was associated with the incidence of ROP [odds ratio: 0.446, 95% confidence interval (CI): 0.332-0.576, $p<0.001$] and BPD [odds ratio: 0.428, 95% CI: 0.316-0.555, $p<0.001$]. The type of lipid emulsion had no statistically significant effect on any other neonatal morbidity. **Conclusions:** Both fish oil-containing and soybean oil-based parenteral lipid emulsions are safe and well-tolerated by preterm infants. However, the use of the SMOF lipid emulsion did not significantly reduce the incidence of cholestasis, ROP and BPD in VLBW infants.

Key Words: very low birth weight infants, fish oil, cholestasis, retinopathy of prematurity, bronchopulmonary dysplasia

INTRODUCTION

Very low birth weight (VLBW, birth weight <1500 g) infants require several weeks to achieve full enteral feeding and have early dependence on parenteral nutrition (PN).[1] With the improvement of neonatal care in recent years, the survival rate of premature infants has increased; thus, the incidence of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) is increasing worldwide.[2] In addition, continuous PN can also lead to parenteral nutrition-associated cholestasis, which may worsen into liver failure.[3,4] Soybean oil-based lipid emulsions are recommended products for parenteral lipid infusion in preterm infants.[5-7] Soybean oil-based lipid emulsions are rich in proinflammatory ω-6 long-chain polyunsaturated fatty acids (LCPUFAs) and phytosterols, both of which can trigger parenteral nutrition-associated liver disease (PNALD).[8,9] Since the side effects of PN on liver function are attributed to the specific properties of soybean oil, some research has focused on reducing excess ω-6 LCPUFA and phytosterols in the lipid emulsion by mixing alternative oils (such as olive oil) and fish oil, which can provide ω-3 LCPUFA to counteract the inflammatory ω-6 LCPUFA effect.[6] It was reported that infants treated with a fish oil-based lipid emulsion specifically for intestinal failure showed significant improvement in liver function.[10,11] Thus, the mixed lipid emulsion consisting of soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil (SMOF) are preferred in 70% of neonatal intensive care unit (NICUs) in the United Kingdom. In China, this approach has only seen pediatric clinical use over the last 3-4 years.

It has been reported that parenteral SMOF is better tolerated, more effective, and safer than soybean oil-based lipid emulsions.[12,13] SMOF contains less ω-6 LCPUFA and phytosterols but more ω-3 LCPUFA than soybean oil-based lipid emulsions.[7,14] The higher availability of ω-

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Manuscript received 15 June 2020. Initial review completed 1 July 2020. Revision accepted 12 August 2020.
doi: 10.6133/apjcn.202009_29(3).0014

3 LCPUFA with SMOF may be considered advantageous with regard to their role in retinal development and anti-inflammation in premature infants. Therefore, parenteral nutrition using SMOF may reduce the incidence of ROP, BPD and cholestasis compared with current standard soybean oil-based lipid emulsions. We hypothesized that PN using SMOF in VLBW infants would reduce the morbidity of cholestasis, ROP and BPD. This study was conducted to compare SMOF with soybean oil-based lipid emulsion as PN in VLBW infants between two time periods, with the primary outcomes being cholestasis, ROP and BPD.

METHODS

Study population

This retrospective study was conducted in the Neonatal Intensive Care Unit of the Children's Hospital of Fudan University. The primary objective was to assess whether SMOF lipid emulsion (Fresenius Kabi, Austria) would reduce cholestasis, ROP and BPD in VLBW infants compared with a soybean oil-based lipid emulsion (lipofundin, B. Braun Melsungen AG, Germany, 50% MCT oil and 50% soybean oil). The secondary objective is to explore the impact on nutrition status and other morbidities. The study period was from June 2017 to June 2018. Eligible participants were very low birth weight infants with birth weight <1500 g admitted to the NICU of the Children's Hospital of Fudan University within 24 hours of birth. Preterm infants who received a single parenteral lipid emulsion formulation for at least 14 consecutive days were included in the study. Patients with congenital chromosomal malformations or congenital major malformations (such as cardiovascular malformations and digestive tract malformations) admitted to our NICU after 24 hours of life or with congenital metabolic problems and biliary tract diseases were excluded. In total, 474 VLBW infants were admitted into our NICU, 232 cases were admitted after 24 hours of life, 88 VLBW infants received parenteral nutrition less than 14 days, and 5 cases were diagnosed with a congenital disease. Preterm infants received PN of a lipid emulsion containing lipofundin from June 30, 2017, to December 31, 2017. SMOF consisting of 30% soybean oil, 30% MCT, 25% olive oil, and 15% fish oil was introduced during the time period from January 1, 2018, to June 30, 2018.

Data collection

Hospital electronic databases (medical records, pathology and imaging) were then accessed to retrieve clinical data from the two cohorts. The study was approved by the Children's Hospital of Fudan University. Anthropometric measurements were taken by the bedside nurse. The primary outcomes cholestasis, ROP and BPD, liver function parameters, and neonatal morbidity were recorded. ROP was screened by indirect ophthalmoscopy starting at 4 weeks of age. BPD was defined as the duration of oxygen supplementation exceeding 28 days. Necrotizing enterocolitis (NEC) was diagnosed clinically or after surgical exploration. Cholestasis was defined as serum-conjugated bilirubin levels of >2 mg/dL (34.2 μmol/L) associated with sustained exposure to PN for ≥14 days.[15] Sepsis was confirmed by blood cultures taken after birth and before any antibiotic treatment. Metabolic bone disease of prematurity was defined as serum total alkaline phosphatase activity above 900 IU/l and serum inorganic phosphate concentrations below 1.8 mmol/l.[16] During hospitalization, elevated levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase [GGT]) were identified. Blood samples were collected weekly as long as PN was required.

Parenteral Nutrition Protocol: PN was started for all VLBW infants on the first day of life in the NICU. Amino acid solution was administered at the rate of 1.5-2.5 g/kg/day on the first day and was increased by 1 g/kg every day up to 3.5 g/kg/day. Lipid emulsions were infused at 0.5 g/kg/day on the first day and increased by 0.5 g/kg every day up to 3.5 g/kg/day. The same trace elements and vitamins were used in both groups.

Statistical analyses

Statistical analyses were performed using R 4.0. Categorical variables are presented as numbers (percentages), while continuous variables are presented as the means (standard deviations [SDs]). Student's t-test was performed to analyze normally distributed data. Chi-square test or Fisher's exact test was used for analysis of categorical variables. Independent variables with p-values less than 0.05 in univariate analysis were selected for multivariate analysis. Multivariate logistic regression analysis was performed after adjustment for possible confounders to identify significant effects of ROP and BPD and to calculate adjusted odds ratios (95%, confidence interval [CI]). The final model retained only significant predictors. Two-sided p values <0.05 were considered statistically significant.

RESULTS

A total of 149 VLBW infants who received parenteral lipid emulsions for at least 14 days were collected during this study, of which 78 infants received soybean lipid-based emulsions and 71 infants received fish oil-based lipid emulsions (SMOF). Demographic characteristics are shown in Table 1. Mean gestational age [28.7 (1.8) vs 28.1 (1.2) weeks; p=0.07] and birth weight [1032.8 (164.6) vs 1023.2 (133.2) grams; p=0.74] did not differ significantly between the two period groups. There were no statistically significant differences in gender or 1- and 5-min APGAR scores.

Breastfeeding was performed along with parenteral feeding. The duration of PN and lipid mass were similar in both groups. Our study showed that both lipid emulsions were safe and well-tolerated in preterm infants. The maximum PN times were 100 days in the soybean oil group and 105 days in the SMOF group. There was no significant difference between the 2 groups of VLBW in mean daily nutrient intake given by PN and individual maximum daily nutrient intake through PN in the first two weeks (Table 2). Comparison of the two groups revealed no significant differences regarding any biochemical parameter (Table 2).

Overall, 12 infants in the soybean oil-based group and 4 infants in the SMOF group developed cholestasis (Table 3). The incidence of cholestasis in the soybean oil-based group (15.4%) was almost triple the incidence in

Table 1. Demographic and clinical characteristics of the study neonates

	ML (n=78)	SMOF (n=71)	*p* value
Mother age, mean, y	31.8 (3.86)	32.0 (3.4)	0.82
Cesarean section, (n)	44 (56.4%)	37 (52.1%)	0.60
Multiple pregnancy, (n)	31 (39.7%)	28 (39.4%)	0.96
Gestational age, mean, wk	28.7 (1.8)	28.1 (1.2)	0.07
Male sex, (n)	37 (47.4%)	30 (42.2%)	0.53
Apgar-1 min, mean	7.1 (1.7)	6.6 (1.9)	0.11
Apgar-5 min, mean	8.4 (0.98)	8.0 (1.1)	0.11
Birth weight, mean, g	1033 (164.6)	1023 (133.2)	0.74
Antenatal steroids, (n)			0.77
Yes	65 (83.3%)	61 (85.9%)	
No	9 (11.5%)	8 (11.3%)	
Unknown	4 (5.1%)	2 (2.8%)	
SGA, (n)	7 (9.0%)	4 (5.6%)	0.44

Continuous data are presented as the mean and standard deviation in parentheses and were tested using Student's t-test. Categorical data are presented as numbers with percentages in parentheses and were tested using the Chi-square test.

Table 2. Parenteral nutritional intake in the first two weeks and serum levels of selected biochemical parameters

	ML (n=78)	SMOF (n=71)	*p* value
First week			
Days from birth to starting enteral nutrition, days	1.7 (1.2)	2.3 (3.2)	0.10
Amino acid mean dose, g/kg/d	3.02 (0.34)	3.07 (0.39)	0.38
Amino acid max dose, g/kg/d	3.52 (0.85)	3.66 (0.41)	0.17
Fat mean dose, g/kg/d	1.48 (0.37)	1.49 (0.37)	0.80
Fat max dose, g/kg/d	2.55 (0.63)	2.62 (0.51)	0.52
Glucose mean dose, g/kg/d	6.70 (1.23)	6.81 (1.06)	0.55
Glucose max dose, g/kg/d	8.07 (2.01)	7.98 (1.60)	0.75
Second week			
Amino acid mean dose, g/kg/d	3.27 (0.52)	3.27 (0.64)	0.99
Amino acid max dose, g/kg/d	3.44 (0.70)	3.53 (0.58)	0.38
Fat mean dose, g/kg/d	2.21 (0.81)	2.33 (0.79)	0.38
Fat max dose, g/kg/d	2.74 (2.25)	2.95 (2.62)	0.58
Glucose mean dose, g/kg/d	6.78 (2.05)	6.72 (1.59)	0.83
Glucose max dose, g/kg/d	7.96 (2.33)	7.93 (1.95)	0.93
Liver function (peak levels in the first four weeks)			
TB, μmol/L	68.9 (35.7)	57.4 (34.1)	0.10
DB, μmol/L	13.2 (6.5)	13.5 (8.5)	0.91
ALT, IU/L	10.4 (5.2)	12.7 (8.3)	0.35
AST, IU/L	32.1 (15.6)	33.6 (14.9)	0.74
GGT, IU/L	105 (60.9)	106 (58.4)	0.98
TBA, μmol/L	31.5 (14.5)	26.1 (11.9)	0.16
PALB, mg/L	73.3 (24.8)	73.7 (20.1)	0.92
ALB, g/L	29.6 (3.3)	29.7 (2.8)	0.85

TB: Total bilirubin; DB: Direct bilirubin; ALT: Alanine transaminase; AST: Aspartate transaminase; GGT: gamma glutamyl transpeptidase; TBA: Total bile acid; PALB: Prealbumin; ALB: Albumin.
Values are expressed as the mean and standard deviation in parentheses and were tested using Student's t-test.

Table 3. Clinical outcomes between the two groups

	ML(n=78)	SMOF (n=71)	*p* value
Cholestasis, n	12 (15.4%)	4 (5.6%)	0.055†
ROP, n	37 (47.4%)	43 (60.1%)	0.19§
BPD, n	42 (53.8%)	54 (76%)	<0.01§
Sepsis, n	35 (44.9%)	31 (43.7%)	0.88§
NEC, n	12 (15.2%)	6 (8.4%)	0.20§
Metabolic osteopathy, n	8 (10.1%)	12 (16.9%)	0.24§
PN duration, mean, days	36.1 (14.1)	37.8 (13.6)	0.57¶
Rate of weight gain, mean, g/d	12.7 (4.1)	13.1 (4.5)	0.59§
Death, n	3 (3.8%)	1 (1.4%)	0.36†

ROP: Retinopathy of prematurity; BPD: Bronchopulmonary dysplasia; NEC: Necrotizing enterocolitis; PN: Parenteral nutrition.
†Fisher's exact test §Chi-square test ¶Student's t-test

the SMOF group (5.6%), but the difference was not statistically significant. Similar results were observed for the incidence of NEC. The incidence of NEC in the soybean oil-based group (15.2%) was almost twice the incidence in the SMOF group (8.4%), and the difference was not statistically significant (Table 3).

The incidence rates of ROP and BPD were high: 47.4% and 53.8% in the soybean oil group and 60.1% and 76% in the SMOF group, respectively (Table 3). The incidence of ROP was not significantly different between the soybean oil group and the SMOF group. However, a significant difference (p=0.01) was observed in the incidence of BPD between the soybean oil group and the SMOF group (Table 3). To further examine the factors affecting the incidence of ROP and BPD, we performed multivariate logistic regression analysis. The results revealed that gestational age was directly associated with the incidence of ROP and BPD (p=0.0003 and p=0.0002, respectively) (Figure 1A and B). Sepsis morbidity, mortality and weight gain during hospitalization in preterm infants were also not significantly different between the two groups (Table 3).

DISCUSSION

This retrospective study in VLBW infants showed that compared with a soybean oil-based lipid emulsion, a mixed lipid emulsion composed of soybean oil, MCT, olive oil, and fish oil did not significantly reduce the incidence of cholestasis, ROP and BPD. We also found no significant effect on parameters such as NEC and sepsis. The safety and tolerability of SMOF are consistently mentioned in the literature. In our study, these two lipid emulsions were well tolerated in preterm infants, but SMOF did not significantly increase the weight gain rate compared to soybean oil-based lipid emulsion. Supplementation of fish oil-containing SMOF during parenteral

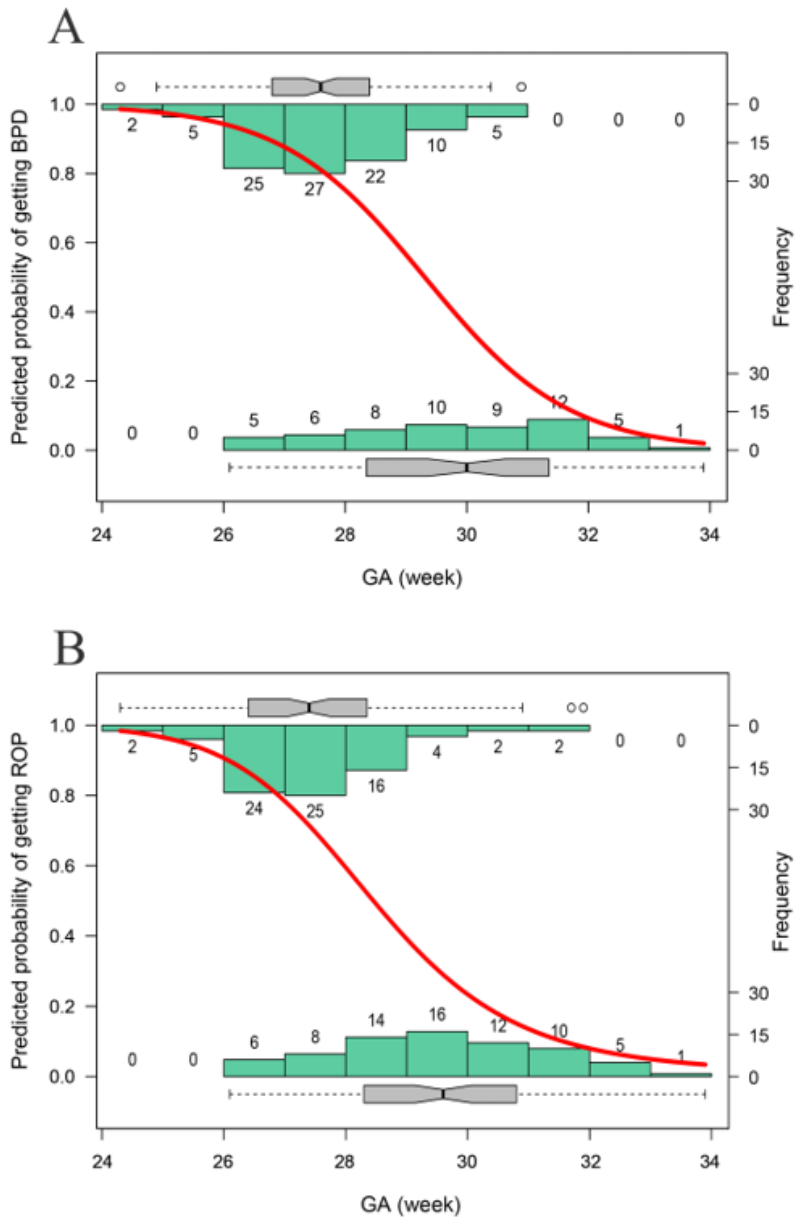

Figure 1. Relationship between gestational age and incidence of ROP (A) and BPD (B) in preterm infants. The incidence rates of ROP (A) and BPD (B) in preterm infants decreases with increasing gestational age. The red curves indicate the predicted probabilities of ROP or BPD by logistics regression, the boxplots indicate the distribution of gestational age, and the histograms indicate the numbers of preterm infants at different gestational ages.

nutrition has been reported to increase EPA and DHA and to decrease arachidonic acid; however, SMOF does not reduce morbidity or affect growth.[16] In particular, it should be noted that the gestational age of preterm infants was relatively low in the present study, which was a major contributing factor to the high incidence of ROP and BPD.[17-19] In addition, the duration of PN reported in the literature was generally 3 weeks,[20-22] and the mean duration of PN in our study was more than 5 weeks (Table 1), indicating that both lipid emulsions were safe for preterm infants, although no significant improvement in outcomes was found.

SMOF is a recently used product relative to soybean oil-based lipid emulsions, and its key ω-3 LCPUFA, docosahexaenoic acid (DHA), improves supply while decreasing soybean oil exposure and plant sterol exposure.[7] Thus, ω-3 LCPUFA DHA has been included in ROP models as a nonoxygen regulator.[23] Fish oil supplementation is recommended to improve DHA enrichment in the retina and thus prevent ROP.[23] SMOF provides not only DHA but also vitamin E, which is known to prevent ROP.[6,24] Beken et al reported that SMOF significantly reduced any stage of ROP.[25] The study by Pawlik et al showed that the combination of pure fish oil lipid emulsion and soybean oil-based lipid emulsion significantly prevented severe ROP.[26] Recently, a retrospective study in Taiwan also found that a fish oil-based mixed emulsion formulation was associated with a reduced incidence of ROP.[27] In the present study, we did not find a significant improvement in ROP incidence. A trial by Collins et al (using a large amount of fish oil) showed no effect on ROP.[28] A recent randomized controlled trial that investigated the effect of SMOF on PNALD also showed no effect against any stage of ROP.[22]

BPD is a long-term complication in preterm infants and has significant impacts on outcomes and quality of life in preterm infants. BPD may also be affected by SMOF interventions; however, the effects used vary widely. Some randomized controlled trial (RCTs) have also found no difference in BPD between SMOF and soybean oil-based lipid emulsions.[13,22,25,29,30] However, Collins et al reported their trial of fish oil supplementation in preterm infants and found a significantly increased risk of BPD.[28] Similar results were obtained for BPD incidence in our study (Table 2). Recently, a meta-analysis study indicated that no specific lipid emulsion (LE) with or without fish oil was superior to another LE in preventing ROP, BPD, cholestasis, growth, mortality, and other neonatal outcomes. There is currently insufficient evidence from randomized studies to determine whether fish oil LE has an advantage in preventing or resolving any clinical outcome.[31-33]

While our study showed that SMOF did not significantly prevent ROP and BPD in VLBW, our results did not indicate a lack of efficacy for cholestasis and sepsis, as we did find that SMOF reduced the incidence of cholestasis and sepsis to some extent (Table 2), although the difference was not statistically significant, which may be due to the small sample size and requires further investigation. In addition, another limitation of this study is that the composition of the two lipid emulsions was not significantly different, which may also have had an impact on examining the improvement of prognosis by fish oil. However, clinical trials to date have not provided sufficient evidence that lipid emulsions containing fish oil improve clinical outcomes such as ROP, BPD, or cholestasis. Further studies with larger well-designed trials are needed to evaluate the ideal composition of lipid emulsion in preterm infants and the roles of fish oil and other lipid emulsions in preventing and alleviating ROP, BPD, and other clinical outcomes.

Conclusion

In this study, soybean oil- and fish oil-based lipid emulsions were found to be safe and well-tolerated in preterm infants. Although this study found that SMOF was able to reduce the incidence of cholestasis and NEC to some extent, it had no significant effect on outcomes such as ROP and BPD. Further optimization of lipid emulsion formulation and randomized controlled studies based on large sample sizes are necessary in the future.

ACKNOWLEDGEMENTS

We would like to express our special thanks to Mr. Peng Shi for his contribution in the data statistical analysis.

AUTHOR DISCLOSURES

There is no potential conflict of interest for this study. This research did not receive any financial support or any other funding.

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