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Low-Dose Intravenous Soybean Oil Emulsion for Prevention of Cholestasis in Preterm Neonates

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Abstract

Background—Premature infants depend on intravenous fat emulsions to supply essential fatty acids and calories. The dose of soybean-based intravenous fat emulsions (S-IFE) has been associated with parenteral nutrition associated liver disease. This study's purpose was to determine if low dose S-IFE is a safe and effective preventive strategy for cholestasis in preterm neonates.

Materials and Methods—This is a multicenter randomized controlled trial in infants with a gestation age (GA) < 29 weeks. Subjects < 48 hours of life were randomized to receive a low (1g/kg/day) or control dose (approximately 3g/kg/day) of S-IFE. The primary outcome was cholestasis, defined as a direct bilirubin > 15% of the total bilirubin at 28 days of life (DOL) or full enteral feeds, whichever was later, after 14 days of parenteral nutrition. Secondary outcomes included growth, length of hospital stay, death, and major neonatal morbidities.

Results—136 neonates (67 and 69 in the low and control group, respectively) were enrolled. Baseline characteristics were similar for the two groups. When the low group was compared to the control group, there was no difference in the primary outcome (69% vs. 63%, 95% CI (−0.1, 0.22), $p=0.45$). While the low group received less S-IFE and total calories over time compared to the control group ($p<0.001$ and $p=0.03$, respectively) weight, length and head circumference at 28 DOL, discharge, and over time were not different ($p>0.2$ for all).

Conclusion—Compared to the control dose, low dose S-IFE was not associated with a reduction in cholestasis or growth.

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Keywords

parenteral nutrition associated liver disease; growth; prematurity

Introduction

Care for extremely low birth weight neonates would be impossible without parenteral nutrition (PN). PN provides hydration and nutrition to those who are unable to tolerate sufficient enteral intake. While PN is life sustaining, it is associated with parenteral nutrition associated liver disease (PNALD), the hallmark of which is cholestasis, a serum direct hyperbilirubinemia. Premature neonates are at high risk for PNALD secondary to prolonged PN exposure, an immature liver, small for gestational age, sepsis, necrotizing enterocolitis, and short bowel syndrome.^{1,2}

The mechanism of liver injury in the premature population is poorly understood and multifactorial. Cohort studies have associated the dose of soybean-based intravenous fat emulsions (S-IFE) with PNALD.^{3–9} S-IFE dose is directly related to serum phytosterol and fatty acid concentrations—which in turn are linked to PNALD.^{10–16} Increasing concentrations of serum phytosterols decrease bile flow.¹³ S-IFE is predominately composed of omega-6 fatty acids, some of which are known to cause inflammation.^{12,16} As fat accumulates in hepatic cells, phagocytic dysfunction and impaired endotoxin clearance occurs.¹⁰ Consequently, a reduced dose of S-IFE may protect against cholestasis. The goal of this study was to determine if a lower dose of S-IFE safely prevents cholestasis in preterm neonates.

Patients and Methods

Study Procedures and Methods

Infants with a gestational age (GA) of ≥ 29 weeks and < 48 hours of age were eligible for enrollment. Exclusion criteria included known chromosomal abnormality, congenital intrauterine infection, structural liver abnormality, and terminal illness. Informed consent was obtained from parents/legal guardians. Each site's investigational review board approved the study.

The lead site for this study was Yale University. Two S-IFE formulations were used in this study (Liposyn II® 20%, Abbott laboratories, Chicago, IL at Yale University and Intralipid® 20%, Fresenius Kabi, Uppsala, Sweden at the University of California, Los Angeles and Northwestern University). Assignment to treatment group was by sequentially numbered, sealed opaque envelopes containing computer generated random numbers with a block size of four. Randomization was stratified by GA (< 27 weeks, ≥ 27 weeks) and site. S-IFE was prescribed by the primary medical team and advanced per routine practice. In general, the control group's S-IFE was advanced by 0.5–1g/kg/day to a target dose of approximately 3g/kg/day while the low group received a maximum S-IFE dose of 1g/kg/day. PN prescription and PNALD screening were according to routine practice. The primary medical team had the option to reduce the subject's S-IFE if the subject developed

hypertriglyceridemia (serum triglyceride concentration > 200 mg/dL) and/or hyperglycemia (serum glucose concentration > 150–200 mg/dL). Once the hypertriglyceridemia and/or hyperglycemia resolved, the S-IFE was increased per protocol. Glucose infusion rates (GIR) were adjusted by the primary medical to maintain normoglycemia and reach a desired total calorie goal. For subjects in the control arm, the S-IFE dose, at the discretion of the primary team, could be reduced to approximately 1.5 g/kg/d if the subject was receiving > 75% of his/her calories from enteral nutrition. PNALD screening consisted of weekly serum bilirubin concentrations if the subject was on PN for > 14 days for the duration of PN. The study was not masked. Full enteral feeds were defined as PN discontinuation.

Study Outcomes

We hypothesized that a reduced dose of S-IFE would safely prevent cholestasis. The primary outcome was cholestasis (serum direct bilirubin (DB)/total bilirubin (TB) > 15% after 14 PN days) at DOL 28 or full enteral feeds, whichever was later. Secondary outcomes included mortality, length of stay, incidence of major neonatal morbidities and anthropometric velocities at DOL 28 and discharge. Bronchopulmonary dysplasia (use of supplemental oxygen at 36 weeks postmenstrual age), late onset sepsis (a culture confirmed blood stream infection after 72 hours of life), necrotizing enterocolitis, and retinopathy of prematurity requiring laser treatment were recorded.

A data safety monitoring board (DSMB) met when approximately 30% and 70% of the subjects completed the study to assess the primary outcome and safety outcomes (mortality, length of stay, chronic lung disease or death, and liver function tests at specific time points). If there was a significant difference (> 2 SD) between the two groups, the DSMB could stop the study.

Statistical Analysis

The frequency of the primary outcome at the lead site prior to the start of the study was approximately 50%. In order to detect a decrease in the incidence of the primary outcome by 50% with 80% power, a sample of 65 infants per arm was required, assuming a two sample chi-squared test with a two-sided 0.05 level significance. To account for early deaths and loss to follow up, the sample size was increased to 136 total subjects.

Categorical variables were examined using the chi-square or Fisher's exact test. For continuous variables, differences were assessed using the Student's t or Wilcoxon rank sum test. To compare growth and laboratory values longitudinally, generalized estimating equation (GEE) models with an autoregressive correlation structure were utilized. For DB, values were transformed using a log of x +1 transformation. The terms of the GEE models were time, group, and group/time interaction. Logistic regression was used to examine the effects of group, lipid product, and group/lipid product interaction on the primary outcome. To examine the relationship between S-IFE dose and maximum DB, a Spearman correlation coefficient was calculated. A pattern mixture model was used to analyze longitudinal DB measurements while adjusting for missing data due to death and dropouts. This analysis was carried out by classifying patients into three subgroups: healthy (PN duration < 28 days and survived to discharge), unhealthy (PN duration > 28 days and survived to discharge), and

non-survivors. A linear mixed effects model with estimates for time, group, and site effects was fit for each subgroup. Interaction effects were examined. A borderline significant interaction between time and site was observed in the unhealthy subgroup. This interaction term was entered into the model. The final estimate for each variable was a weighted sum of the estimates from the three subgroups. A bootstrap resampling technique was then performed within each of the subgroups to impute meaningful values to assess the missing data effect. Statistical analyses were performed in SAS 9.3 (SAS Institute, Cary NC). P-values <0.05 were considered statistically significant. The analysis was performed as intention-to-treat.

Results

From May 2009 to November 2012, 136 infants were enrolled. Sixty-five neonates in the low group, and 62 neonates in the control were included in the analysis. One subject was lost to follow-up. Four subjects in the low group and five subjects in the control group, including the subject lost to follow-up, did not have laboratory data available for analysis of the primary outcome (Figure 1). Baseline data were similar between the two groups with the exception of antenatal steroids (Table 1).

S-IFE dose, GIR, and total (parenteral plus enteral) calories over time were significantly different between the two groups. On average over time, the low group had 0.5 g/kg/day less S-IFE than the control group (95% CI (0.4, 0.6), $p < 0.001$). At study days 7, 14, 21, and 28, the S-IFE dose was significantly less in the low group vs. control group ($p < 0.001$ each). On average over time, the low group's GIR was 0.6 mg/kg/min higher than the control group (95% CI (0.14, 1.03), $p = 0.01$). At study days 7 and 14, the low group had a higher GIR compared to the control group ($p = 0.03$ each). The low group received roughly 3.3 kcal/kg/day less total calories over time when compared to the control group (95% CI (0.4, 6.2), $p = 0.03$). Total calories were decreased in the low group compared to the control group at study day 7 ($p = 0.04$), but not at days 14 ($p = 0.8$), 21 ($p = 0.2$), and 28 ($p = 0.2$). (Figure 2A–C). The estimated mean difference in amino acid dose over time between the two groups was not statistically different (0.12 g/kg/d higher in the low group, 95% CI (0.08, 0.31), $p = 0.3$).

The estimated mean increase over time for S-IFE, GIR, parenteral calories, and amino acid dose in the groups was 0.7 g/kg/day ($p < 0.001$), 0.04 mg/kg/min ($p < 0.01$), 2 kcal/kg/day ($p < 0.001$), and 0.2 g/kg/day ($p < 0.001$), respectively. The interaction between group and time was not statistically significant for GIR, parenteral calories, and amino acid dose. However, the interaction for S-IFE was significant indicating that for each additional time-point the difference between the two groups increases with an estimated coefficient of 0.06 g/kg/day (95% CI (0.04, 0.07), $p < 0.001$).

Feeds were started in both groups on median DOL 5 (range 2–22 for the low group, 2–25 for the control group, $p = 0.7$). Discontinuation of feeds for > 72 hours once enteral nutrition was started and prior to PN discontinuation was not significantly different between the low group and control group (38% vs. 40% $p = 0.6$). Ten percent and 8% of the low and control group had a major abdominal surgery ($p = 0.6$). Sixteen percent in the low group and 11% in the

control group developed necrotizing enterocolitis ($p=0.5$). Median PN duration was 20 (range 7–135) and 18 (range 8–116) days for the low and control group, respectively ($p=0.6$). There was no difference between the low group and control group with regards to the percentage of subjects receiving PN at day of life 14 (82% vs. 78%, $p=0.6$), 21 (52% vs. 41%, $p=0.2$), or 28 (27% vs. 29%, $p=0.8$). At day of life 14, 57% of the control subjects who were alive and receiving PN received 2.5 g/kg/d of S-IFE.

The primary outcome did not differ significantly between the groups. In the low group, 45 out of 65 infants (69%) developed a DB/TB 15% after 2 weeks of PN. In the control group, 39 out of 62 (63%) achieved this endpoint ($p=0.45$) (Table 2). Eight percent vs. 11% of the low and control group had a DB > 2 mg/dL ($p=0.6$). The estimated mean difference over time for DB between the low and control group was 0.04 mg/dL (95% CI (−0.02,0.1), $p=0.3$) (Figure 3). When a pattern mixture model was performed accounting for informative missing data, the results remained non-significant at 0.03 mg/dL (95% CI (−0.01,0.06) $p=0.1$). A bootstrapping model yielded a group difference estimate of 0.04 mg/dL (95% CI (−0.02,0.11), $p=0.2$). DB concentrations and liver function tests were not significantly different between the two groups (Table 2). The median maximum DB in the low group (0.6 mg/dL, range 0.3–9.4) was similar to the control group (0.5 mg/dL, range 0.1–5.2) ($p=0.6$) (Table 2). Maximum DB was not correlated with the average lipid dose (Spearman correlation coefficient=−0.06, $p=0.5$). The median triglyceride concentration (IQR) was lower in the low group compared to the control group (46 (34,83) vs. 88 mg/dL (67,146), $p<0.001$).

With regards to S-IFE product received, 97 subjects received Liposyn II® 20% at Yale University and 39 subjects received Intralipid® 20% at the other two sites (37 subjects at the University of California, Los Angeles and two subjects at Northwestern University). The primary and secondary outcome by S-IFE product and group are provided in the Appendix (Table 1). This subgroup analysis did not reveal a statistical difference between low group and control group with regards to the primary and secondary outcomes and other liver function tests. Subjects who received Liposyn II® 20% in comparison to those who received Intralipid® 20% were more likely to develop the primary outcome ($p=0.002$) and be diagnosed with bronchopulmonary dysplasia ($p=0.004$) and less likely to be diagnosed with retinopathy of prematurity ($p=0.006$) (Appendix, Table 1). However, the interaction between lipid product and group was not statistically significant (OR 0.95, 95% CI (0.43, 2.14), $p=0.95$), indicating that the effect of the intervention was not dependent on the lipid product.

There was no difference in growth velocity, mortality (9% vs. 7%, $p=0.5$), or major neonatal morbidities such as bronchopulmonary dysplasia (38% vs. 40%, $p=0.7$), late onset sepsis (9% vs. 4%, $p=0.5$), or retinopathy of prematurity requiring laser (13% vs. 10%, $p=0.6$) between the low and control group, respectively. The estimated mean weight difference over time between the low and control group was 33 g (95% CI (−68,134), $p=0.5$). There was no difference over time for length or head circumference growth between the two groups (Figure 4A–C).

Discussion

In this multi-site randomized controlled trial, approximately 1 g/kg/day when compared to a higher dose of S-IFE did not reduce the incidence of cholestasis in preterm neonates. Moreover, liver function tests and DB values were similar between the groups (Table 2). Our study implies that in a population of preterm infants whose median PN duration is relatively short, S-IFE dosage does not significantly contribute to the pathogenesis of cholestasis. Supporting the results of our study, there was no difference in the incidence of cholestasis in a retrospective study by Nehra *et al* that compared 1 g/kg/day vs. 2–3 g/kg/day of S-IFE in neonates with gastrointestinal disorders. However, the percent DB change over time, while not statistically significant, was decreased in the low group vs. controls ($p=0.05$).¹⁷ Contrary to our study and the aforementioned study by Nehra *et al*, Sanchez *et al* reported a reduction in PNALD incidence in surgical neonates who received 1 g/kg/day of S-IFE when compared to a historical cohort who received 2 g/kg/day of S-IFE (22% vs. 43%).^{6,17} In another study, surgical neonates with cholestasis who received 1 g/kg of S-IFE twice a week were more likely to exhibit PNALD resolution (10% vs. 42%), but more likely to develop a mild essential fatty acid deficiency when compared to a historical cohort who received 3 g/kg/day of S-IFE.⁴ While the current study did not measure essential fatty acid profiles, it would be unlikely that our subjects developed an essential fatty acid deficiency considering that preterm neonates require a minimum 0.25 g/kg/day of S-IFE to prevent a deficiency.¹⁸

Beyond the concern of an essential fatty acid deficiency, there is a concern that infants that receive less lipid calories will not grow well and long-term neurodevelopment could be affected. Studies have not associated 1 g/kg/day of an intravenous fatty acid emulsion with a decrease in growth when compared to those who receive the standard S-IFE dose.^{3,4,6,17} One of the major results of our investigation was that there was no difference in growth between the two groups (Table 2, Figure 4). It is important to note that the similar growth patterns appreciated between the two study groups may be explained by sample size and/or a higher GIR in the low group vs. control group (Figure 2B). However, a mean GIR increase of 0.6 mg/kg/min over time in the low group may not be sufficient by itself to account for this lack of difference.

Any interventional study aimed at preventing PNALD must target a population at high risk for PNALD. The current study enrolled infants with a GA ≥ 29 weeks. It was assumed that this group would be prescribed a relatively prolonged PN course. Possibly due to a more intense approach to enteral nutrition, the median PN duration was slightly less than three weeks in both groups. Future studies should target neonates with congenital gastrointestinal disorders and/or premature neonates requiring small bowel resection who would be exposed to longer periods of PN and S-IFE.

A short duration of PN and S-IFE was one of the major limitations of our study. As a result, the study's incidence of a direct bilirubin > 2 mg/dL was approximately 10%. In addition, because many subjects were receiving a significant amount of enteral nutrition in the first couple of weeks of life or weaned off PN entirely, only 57% of controls subjects received 2.5 g/kg/d of S-IFE at day of life 14. An increased incidence of hypertriglyceridemia may

have also prevented the control group from reaching their target dose considering that the control group's initial triglyceride concentration was significantly higher than the low group's initial triglyceride concentration. Also, the protocol allowed clinicians to reduce the S-IFE dose if a control subject was noted to be hyperglycemic. While the inability of all control subjects to reach a target of 3 g/kg/d of S-IFE is a study limitation, we believe this reflects daily clinical practice, and it would be unethical for the study team to require that a control subject with hypertriglyceridemia, hyperglycemia, or who is receiving a significant amount of enteral nutrition to be prescribed 3 g/kg/d of S-IFE.

Lastly, some subjects had missing data (Table 2). To investigate the effect of informative missing data with regards to DB over time, a pattern mixed model with bootstrapping was used. P-values from this model were similar to the GEE model.

Other study limitations include the use of two different S-IFE products and the fact that the study was not masked. Liposyn II® 20% is composed of 50% safflower and 50% soybean oil, while Intralipid® 20% is entirely composed of soybean oil. The polyunsaturated fatty acid and phytosterol content, however, are relatively similar (Table 2, Appendix).¹⁹ It remains unclear if the observed increased incidence of the primary outcome and bronchopulmonary dysplasia and decreased incidence of retinopathy of prematurity in the Liposyn II® group in comparison to the Intralipid 20%® group is because the type of S-IFE, site, and/or unknown reasons. With regards to the primary outcome, the effect of the interaction between the lipid product and group was not statistically significant (OR 0.95, 95% CI (0.43, 2.14), $p=0.95$). Also, there was no statistical difference between the primary and secondary outcomes and other liver function tests when these variables were compared by group according S-IFE product. Lastly, the Liposyn II® group weighed significantly less at birth in comparison to the Intralipid 20%® group. This may explain not only the increased incidence of bronchopulmonary dysplasia, but also the trend for an increase in mortality and necrotizing enterocolitis in this group (Appendix, Table 1). Considering the study's sample size, risk for a Type I error with a post-hoc analysis, and the well-known influence of site on specific clinical outcomes, one should be cautioned to draw any firm conclusions regarding S-IFE product and specific outcomes.

In order to mask the study, S-IFE would have to be placed in the PN bag. Three-in-1 solutions are associated with an increased risk for infection and may interfere with one's ability to detect a precipitate.²⁰ As a result, a masked study was not feasible. An unmasked study may more accurately reflect what is done in clinical practice when an infant is prescribed low dose S-IFE (*i.e.* optimize GIR or enteral nutrition). It remains unclear if clinicians increased the GIR in the low group because they were biased by group assignment or if these subjects were more glucose tolerant. The higher GIRs in the low group may account for the lack of difference in growth between the two groups and, at the same time, may have counteracted any protective effect of low dose S-IFE.

Last, the definition of cholestasis in this study is different than the definition commonly used by other studies.³⁻⁵ Suchy *et al*^{21,p. 389} stated that "the conjugated fraction of serum bilirubin in neonates should be no higher than 15% of than the total serum bilirubin concentration." This definition was used to catch the subgroup of subjects who would

develop some degree of liver dysfunction without a DB > 2mg/dL. Many clinicians believe an absolute number rather than a ratio is a more clinically relevant and accurate predictor of morbidity and mortality. In a post-hoc analysis, there was no difference between the two groups with regards to the percent of subjects who had a DB > 2 mg/dL or maximum DB (Table 2). In order to power a study to detect a meaningful difference between two groups for the incidence of a DB > 2 mg/dL, a prohibitive sample size would be required that would not have been possible for this study.

Conclusion

In conclusion, in this randomized, unmasked, controlled trial, a lower dose of S-IFE did not prevent cholestasis in babies with a GA < 29 weeks. Growth between the two groups was similar. Considering the possible unknown and undetected risks associated with intravenous lipid sparing, specifically with regards to essential fatty acid deficiencies, growth and neurodevelopment, this prevention strategy cannot be currently recommended for routine practice for premature neonates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DB	direct bilirubin
DOL	days of life
GA	gestational age
GIR	glucose infusion rate
GEE	generalized estimating equation
S-IFE	soybean-based intravenous fat emulsion
TB	total bilirubin
PNALD	parenteral nutrition parenteral nutrition associated liver disease

References

1. Christensen R, Henry E, Wiedmeier S, Burnett J, Lambert D. Identifying patients, on the first day of life, at high-risk of developing parenteral nutrition-associated liver disease. *J Perinatol*. 2007; 27:284–290. [PubMed: 17344923]

2. Cole CR, Hansen NI, Higgins RD, Ziegler TR, Stoll BJ. Very low birth weight preterm infants with surgical short bowel syndrome: incidence, morbidity and mortality, and growth outcomes at 18 to 22 months. *Pediatrics*. 2008; 122:e573–e582. [PubMed: 18762491]
3. Puder M, Valim C, Meisel JA, et al. Parenteral fish oil improves outcomes in patients with parenteral nutrition associated liver injury. *Ann Surg*. 2009; 250:395. [PubMed: 19661785]
4. Cober MP, Killu G, Brattain A, Welch KB, Kunisaki SM, Teitelbaum DH. Intravenous fat emulsions reduction for patients with parenteral nutrition-associated liver disease. *J Pediatr*. 2012; 160:421–427. [PubMed: 21982303]
5. Premkumar MH, Carter BA, Hawthorne KM, King K, Abrams SA. High rates of resolution of cholestasis in parenteral nutrition-associated liver disease with fish oil-based lipid emulsion monotherapy. *J Pediatr*. 2013; 162:793–798. [PubMed: 23164314]
6. Sanchez SE, Braun LP, Mercer LD, Sherrill M, Stevens J, Javid PJ. The effect of lipid restriction on the prevention of parenteral nutrition-associated cholestasis in surgical infants. *J Pediatr Surg*. 2013; 48:573–578. [PubMed: 23480915]
7. Shin JI, Namgung R, Park MS, Lee C. Could lipid infusion be a risk for parenteral nutrition-associated cholestasis in low birth weight neonates? *Eur J Pediatr*. 2008; 167:197–202. [PubMed: 17436017]
8. Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet J-C, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. *JPEN J Parenter Enteral Nutr*. 2000; 24:345–350. [PubMed: 11071594]
9. Rollins MD, Ward RM, Jackson WD, et al. Effect of decreased parenteral soybean lipid emulsion on hepatic function in infants at risk for parenteral nutrition-associated liver disease: a pilot study. *J Pediatr Surg*. 2013; 48:1348–1356. [PubMed: 23845629]
10. Roth B, Fkelund M, Fan BG, Hagerstrand I, Nilsson-Ehle P. Lipid deposition in kupffer cells after parenteral fat nutrition in rats: a biochemical and ultrastructural study. *Intensive Care Med*. 1996; 22:1224–1231. [PubMed: 9120117]
11. Le HD, de Meijer VE, Robinson EM, et al. Parenteral fish-oil-based lipid emulsion improves fatty acid profiles and lipids in parenteral nutrition-dependent children. *Am J Clin Nutr*. 2011; 94:749–758. [PubMed: 21775562]
12. Skouroliaou M, Konstantinou D, Koutri K, et al. A double-blind, randomized clinical trial of the effect of ω -3 fatty acids on the oxidative stress of preterm neonates fed through parenteral nutrition. *Eur J Clin Nutr*. 2010; 64:940–947. [PubMed: 20551967]
13. Carter BA, Taylor OA, Prendergast DR, et al. Stigmasterol, a soy lipid-derived phytosterol, is an antagonist of the bile acid nuclear receptor FXR. *Pediatr Res*. 2007; 62:301–306. [PubMed: 17622954]
14. Clayton PT, Bowron A, Mills KA, Massoud A, Casteels M, Milla PJ. Phytosterolemia in children with parenteral nutrition-associated cholestatic liver disease. *Gastroenterology*. 1993; 105:1806–1813. [PubMed: 8253356]
15. Bindl L, Lütjohann D, Buderus S, Lentze MJ, Bergmann KV. High plasma levels of phytosterols in patients on parenteral nutrition: a marker of liver dysfunction. *J Pediatr Gastroenterol Nutr*. 2000; 31:313–316. [PubMed: 10997380]
16. El Kasmi KC, Anderson AL, Devereaux MW, et al. Phytosterols promote liver injury and kupffer cell activation in parenteral nutrition-associated liver disease. *Sci Transl Med*. 2013; 5:206ra137.
17. Nehra D, Fallon EM, Carlson SJ, et al. Provision of a soy-based intravenous lipid emulsion at 1 g/kg/d does not prevent cholestasis in neonates. *JPEN J Parenter Enteral Nutr*. 2013; 37:498–505. [PubMed: 22767698]
18. Lee EJ, Simmer K, Gibson RA. Essential fatty acid deficiency in parenterally fed preterm infants. *J Paediatr Child Health*. 1993; 29:51–55. [PubMed: 8461181]
19. Meisel JA, Le HD, de Meijer VE, et al. Comparison of 5 intravenous lipid emulsions and their effects on hepatic steatosis in a murine model. *J Pediatr Surg*. 2011; 46:666–673. [PubMed: 21496535]
20. Scott EM, Gorman SP, Wyatt TD, Magill EA. Growth of microorganisms in total parenteral nutrition mixtures and related clinical observations. *J Clin Hosp Pharm*. 1985; 10:79–88. [PubMed: 3923044]

21. Suchy FJ. Neonatal cholestasis. *Pediatr Rev.* 2004; 25:388–396. [PubMed: 15520084]
22. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. *Pediatrics.* 2010; 125:e214–224. [PubMed: 20100760]

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Clinical Relevancy Statement

Pediatric parenteral nutrition associated liver disease (PNALD) is common complication associated with parenteral nutrition (PN) in preterm neonates. While the dose of intravenous fatty acid emulsions has been implicated as a contributor to PNALD, this study demonstrates that a lower dose of soybean oil does not prevent cholestasis or liver dysfunction in premature neonates.

Figure 1.
Flow diagram for study participants.

Figure 2.

A. S-IFE, B. GIR, and C. Total calories (parenteral and enteral). Data are represented as a mean with the 95% Confidence Interval. Over time, the differences between the groups for S-IFE (95% CI (0.4, 0.6), $p < 0.001$), GIR (95% CI (0.14, 1.03), $p < 0.01$), and calories (95% CI (0.4, 6.2), $p < 0.03$) were significant.

Figure 3.

Direct bilirubin. Data are represented as a mean with the 95% Confidence Interval. Over time, the difference between the two groups for direct bilirubin was not statistically significant (95% CI (-0.02,0.1), $p=0.3$).

Figure 4.

A. Weight, B. Length, C. Head circumference. Data are represented as a mean with 95% Confidence Interval. Over time, the differences between the groups for weight (95% CI (-51.5,134.1), $p=0.5$), length (95% CI (-0.78, 1.76), $p=0.5$), and head circumference (95% CI (-0.57,0.86), $p=0.7$) were not significant.

Table 1

Baseline characteristics for the low group and control group. Data are represented as a mean ($\pm$ SD) or n (percentage). Small for gestational age was defined as $< 10^{\text{th}}$ percentile.²²

	Low Group n=69	Control Group n=67	p-value
Gestational age (weeks)	27 $\pm$ 2	26 $\pm$ 2	0.6
Birth weight (g)	904 $\pm$ 279	930 $\pm$ 286	0.6
Race—Caucasian	49 (71%)	41 (61%)	0.1
Ethnicity—Hispanic	11 (16%)	16 (24%)	0.3
Delivery mode—Cesarean section	54 (78%)	43 (64%)	0.1
Apgar at 1 minute < 4	25 (36%)	14 (21%)	0.05
Apgar at 5 minute < 4	4 (6%)	1 (2%)	0.4
Maternal antenatal steroids	68 (99%)	60 (90%)	0.03
Maternal intrapartum antibiotics	20 (29%)	24 (36%)	0.4
Small for gestational age	17 (25%)	11 (16%)	0.2
Multiple gestation	21 (30%)	13 (19%)	0.4

Table 2

Primary outcome, liver function, and growth. Data is represented as n (percentage), median (IQR), mean ($\pm$ SD). Sample size is indicated next to each variable.

	Low Group (n=69)	Control Group (n=67)	p-value (95% CI)
Primary outcome (65, 62)	45 (69%)	39 (63%)	0.45 (−0.1,0.22)
Other measures of liver function			
Maximum direct bilirubin (mg/dL) (65, 66)	0.6 (0.4,1)	0.5 (0.4,0.8)	0.6 (−0.3,0.5)
28 DOL			
Direct bilirubin (mg/dL) (59, 54)	0.4 (0.3–0.7)	0.4 (0.3–0.7)	0.6 (−0.3,0.5)
Asparate aminotransferase (I/U), (60, 54)	25 (19–33)	27 (20–36)	0.4 (−9.6,10.9)
Alanine aminotransferase (I/U) (57, 52)	10 (6–15)	8 (6–11)	0.3 (−3.4,13.5)
Full enteral feeds			
Direct Bilirubin (mg/dL) (66, 64)	0.4 (0.3–0.7)	0.4 (0.3–0.6)	0.7 (−0.35,0.51)
Asparate Aminotransferase (I/U) (59, 57)	25 (19–32)	26 (20–35)	0.4 (−14,10.9)
Alanine Aminotransferase (I/U) (69, 56)	9 (6–15)	8 (6–11)	0.5 (−4.6,13.5)
Growth			
28 DOL			
Weight (g/week) (67, 61)	63 $\pm$ 39	66 $\pm$ 34	0.6 (−16.5,9.1)
Length (cm/week) (61, 61)	0.9 $\pm$ 0.5	0.8 $\pm$ 0.5	0.4 (−0.1,0.26)
Head circumference (cm/week) (61, 61)	0.6 $\pm$ 0.3	0.5 $\pm$ 0.3	0.8 (−0.09,0.12)
Discharge			
Weight (g/week) at discharge (62, 61)	140 $\pm$ 28	140 $\pm$ 30	1 (−10.6,10.4)
Length (cm/week) (63, 61)	1.1 $\pm$ 0.7	0.9 $\pm$ 0.3	0.1 (−0.04,0.32)
Head circumference (cm/week) (61, 61)	0.8 $\pm$ 0.4	0.7 $\pm$ 0.2	0.5 (−0.08,0.15)