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Low Dose Parenteral Soybean Oil for the Prevention of Parenteral Nutrition Associated Liver Disease in Neonates with Gastrointestinal Disorders: a Multi-Center Randomized Controlled Pilot Study

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Abstract

Background—Neonates with gastrointestinal disorders (GD) are at high risk for parenteral nutrition associated liver disease (PNALD). Soybean-based intravenous lipid emulsions (S-ILE) have been associated with PNALD. This study's objective was to determine if a lower dose when compared to a higher dose of S-ILE prevents cholestasis without compromising growth.

Material and Methods—This multi-center randomized controlled pilot study enrolled subjects with GD who were 5 days of age to a low dose (approximately 1 g/kg/day) (LOW) or control dose of S-ILE (approximately 3 g/kg/day) (CON). The primary outcome was cholestasis (direct

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Conflicts of Interest:

The authors have no conflicts of interest to disclose.

bilirubin (DB) > 2 mg/dL) after the first seven days of age. Secondary outcomes included growth, PN duration, and late onset sepsis.

Results—Baseline characteristics were similar between the LOW (n=20) and CON groups (n=16). When the LOW group was compared to the CON group, there was no difference in cholestasis (30% vs. 38%, $p=0.7$) or secondary outcomes. However, mean ($\pm$ SE) DB rate of change over the first eight weeks (0.07 ± 0.04 vs. 0.3 ± 0.09 mg/dL/week, $p=0.01$) and entire study (0.008 ± 0.03 vs. 0.2 ± 0.07 mg/dL/week, $p=0.02$) was lower in the LOW group when compared to the CON group.

Conclusion—In neonates with GD who received a lower dose of S-ILE, DB increased at a slower rate in comparison to neonates who received a higher dose of S-ILE. Growth was comparable between the groups. This study demonstrates a need for a larger, randomized controlled trial comparing two different S-ILE doses for cholestasis prevention in neonates at risk for PNALD.

Keywords

neonates; parenteral nutrition; cholestasis; soybean oil; gastrointestinal disorders

Introduction

Neonates with congenital and acquired gastrointestinal disorders (GD) are at high risk for parenteral nutrition associated liver disease (PNALD).^{1,2} The mortality for most children with GD is low, and most cases of PNALD are transient.¹ However, in a subpopulation of GD neonates with intestinal failure secondary to short bowel syndrome and/or severe gastrointestinal dysmotility, PNALD is associated with an increased risk for bleeding, impaired hepatic drug metabolism, and portal hypertension followed by liver failure.^{1,2} Advanced PNALD remains the leading cause of mortality for children with GD, and is the most common diagnosis for children awaiting a combined small bowel-liver transplant.^{2,3,4} The goal of transplant is to restore normal liver function and/or obtain enteral autonomy. However, transplants are expensive and associated with a five-year patient and graft survival rate of 65–75%.^{5,6} Moreover, the post-transplant course can be fraught with infections, malignancy, and graft rejection.

Preventative PNALD strategies are lacking and needed. The discontinuation of parenteral nutrition (PN) is the most effective preventative and treatment strategy for PNALD. In some cases, this may not be possible because of gestational age, critical illness, and gastrointestinal anatomy and function. The dose and composition of intravenous lipid emulsions are thought to play an important role in PNALD.^{7–15} Soybean-based intravenous lipid emulsions (S-ILE) are a source of calories and essential fatty acids. The S-ILE products approved by the Food and Drug Administration (FDA) are traditionally dosed at 3 g/kg/day and contain high doses of hepatotoxic and inflammatory phytosterols and polyunsaturated omega-6 fatty acids.^{13,14} By reducing the dose of S-ILE, the liver may be exposed to decreased concentrations of these substances and, therefore, less susceptible to hepatic injury. Neonates with intestinal failure may reap the most benefit from lipid sparing. However, this group is at high risk for failure to thrive, which in turn, is associated with poor

cognitive and behavioral outcomes.^{9,16} Current literature is conflicting as to whether a reduced dose of S-ILE can prevent PNALD without compromising growth.^{7,8,12,17,18} This pilot study's purpose was to demonstrate feasibility and investigate the effect of a reduced dose of S-ILE, when compared to the standard dose of S-ILE, on liver function and short-term growth in GD neonates.

Methods

Study Outcomes

The primary outcome for this preliminary study was cholestasis (serum DB > 2 mg/dL). Secondary outcomes included weight velocity at 28 days of age, PN duration, and late onset sepsis (positive blood culture in infants > 72 hours of age and requiring at least five days of intravenous antibiotics). Tertiary outcomes included maximum serum DB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and triglyceride concentrations, DB > 1 mg/dL, number of days to reach maximum DB, and DB rate of change ((maximum serum DB-baseline DB)/number weeks to reach maximum serum DB). Cholestasis and DB > 1 mg/dL was determined after the first seven days of age and prior to hospital discharge, withdrawal, or death, whichever came first.

Patient Population

Neonates with GD (gastroschisis, omphalocele, small bowel atresia, intestinal perforation, Hirschsprung's disease, volvulus, or meconium ileus and/or peritonitis) and who were ≤ 5 days of age at enrollment were included in this study. Patients with an inability to provide informed consent or who had a primary liver disorder excluding PNALD, congenital intrauterine infection, metabolic disorder, or terminal illness were excluded. Informed, written consent was obtained from all parents/legal guardians. The FDA (IND 122,478) and institutional review boards at each institution approved the study.

Study Procedures and Methods

Randomization was stratified by site and blocks of four using sealed opaque envelopes. Subjects were randomized to either a low (approximately 1 g/kg/day IV, LOW) or the standard dose (approximately 3 g/kg/day IV, CON) of S-ILE (20% Intralipid®, Fresenius Kabi, Uppsala, Sweden) in an unmasked fashion. According to clinical practice in the participating centers, S-ILE was initiated in the first 24–48 hours of age and advanced by 0.5–1 g/kg/day to the target dose depending on triglyceride tolerance. The intervention continued until the subject reached approximately 100 days of age, was weaned from PN, discharged from the hospital, or died, whichever came first. If PN was discontinued and restarted prior to 100 days of age, the subject was prescribed the dose he/she was randomized to.

Subjects received PN comprised of dextrose and amino acids (10% Premasol®, Baxter, Deerfield, IL). Goal calories and amino acid doses for term and low birth weight neonates were approximately 100 and 120 kcal/kg/day and 3 g/kg/day and 3–4 g/kg/day, respectively. Goal glucose infusion rates were increased to a maximum of 12–16 mg/kg/min and adjusted at the discretion of the primary medical team based on glucose tolerance, goal calories, and

growth. Enteral feeds were initiated and advanced per routine care. For CON subjects receiving greater than 50–75% of calories from enteral nutrition, the S-ILE dose could be reduced by approximately 50%. S-ILE could be held or reduced by 50% for hyperglycemia (serum glucose > 200 mg/dL) or hypertriglyceridemia (serum triglyceride concentration > 200 mg/dL). Once hyperglycemia or hypertriglyceridemia resolved, S-ILE was advanced to the target dose.

Study outcomes and adverse events were collected until a subject was discharged from the hospital or died. Adverse events included hyperglycemia (serum glucose > 200 mg/dL for three consecutive measurements separated by two hours) and hypertriglyceridemia (serum triglyceride concentration > 200 mg/dL for two consecutive measurements separated by 24 hours). According to routine practice, serum DB concentrations were measured at least weekly for any neonate on PN for greater than 14 days and/or who developed cholestasis.

At both study institutions, a fish-based intravenous lipid emulsion (Omegaven®, Fresenius Kabi, Bad Homburg, Germany) was available under a research protocol or compassionate use. Because of the institutions' experience with intravenous fish oil and published literature that demonstrates that intravenous fish oil can promote biochemical resolution of PNALD, subjects who were considered high risk for advanced PNALD, could withdrawal from the study to receive fish oil.^{9,10} The decision to withdraw was made by the parents/legal guardians along with consultation with a multi-disciplinary team that included neonatology, pediatric surgery, and/or pediatric gastroenterology. At the time of withdrawal, the study intervention ceased, but data collection continued until hospital discharge.

A Data Safety Monitoring Committee met on an annual basis to review safety outcomes.

Statistical Methods and Analysis

Prior to the start of the study, the incidence of cholestasis at the lead site was approximately 40–45%. In order to detect a 50% reduction in the primary outcome with a type I error of 5% and power of 80%, approximately 60 subjects per arm would be required. Because of a much slower than anticipated enrollment, a preliminary analysis was performed. The analysis revealed that the sample size would not yield a statistically significant difference for the primary outcome between the two arms and that further enrollment would be futile.

Subjects who required an abdominal operation (excluding gastrostomy tubes and rectal biopsies) and received PN for greater than 14 days were included in the final analysis. Categorical variables were examined using the Fisher's exact test. For continuous variables, differences were assessed using the Student's t-test. Repeated measures with an autoregressive covariance structure were used to compare longitudinal data on growth, parenteral and enteral nutrition, and laboratory values. For DB values reported as “non-detectable,” a value of 0.1 mg/dL was assumed. One subject in the LOW group had abnormally high AST and ALT concentrations at the start of the study. When these values were removed from the analyses, the results were qualitatively the same (data not shown).

Statistical analyses were performed with SAS 9.3 (SAS Institute, Cary NC). P-values < 0.05 were considered statistically significant. No adjustments were made for multiple

comparisons. Non-longitudinal data are presented as means $\pm$ SD. Longitudinal data are presented as means $\pm$ SE.

Results

Between October 2010 to February 2014, 41 subjects were enrolled and randomized. Five subjects were excluded because they received ≥ 14 days of PN and/or did not have an abdominal operation. The final analysis included 36 subjects (LOW=20, CON=16) (Figure 1). Baseline characteristics and laboratory values were comparable between the two groups with 75% of subjects in each group being diagnosed with gastroschisis at birth (Table 1). Thirty percent of the LOW group and 38% of the CON developed the primary outcome of cholestasis ($p=0.7$). No difference was demonstrated in any of the secondary outcomes (Table 2). Maximum serum DB (1.5 ± 1.4 vs. 1.9 ± 1.8 mg/dL, $p=0.5$) and time to reach this milestone (25 ± 13 vs. 27 ± 14 days, $p=0.6$) were comparable for the LOW and CON group, respectively. The rate of change for DB, from baseline to the maximum value recorded (0.3 ± 0.08 vs. 0.5 ± 0.09 mg/dL/week, $p=0.2$), and other liver function tests were not significantly different when the LOW group was compared to the CON group. However, the DB rates of change for the first eight weeks (0.07 ± 0.04 vs. 0.3 ± 0.09 mg/dL/week, $p=0.01$) and entire study period (0.008 ± 0.03 vs. 0.2 ± 0.07 mg/dL/week, $p=0.02$) were significantly lower in the LOW group versus the CON group (Table 3 and Figure 2A).

Growth velocity over the first month of age was similar in LOW group when compared to the CON group (18 ± 8 vs. 24 ± 16 g/day, $p=0.3$) (Table 2). Weight change over time and discharge weight, length, and head circumference did not differ between the two groups (Table 2 and 4). Glucose delivery rate ($p=0.6$), parenteral amino acids ($p=0.3$), parenteral calories ($p=0.4$) and enteral calories ($p=0.8$) over time were similar between the two groups (Table 4). As expected, at the start of the first study week, the LOW group received slightly less total parenteral calories (88 ± 2 vs. 100 ± 5 kcal/kg/day, $p=0.08$) and significantly less S-ILE (1 ± 0.01 vs. 2.9 ± 0.1 g/kg/day, $p < 0.001$) than the CON group. For each week on the study, the S-ILE dose decreased by 0.01 ± 0.005 mg/kg/day in the LOW group and 0.2 ± 0.1 g/kg/day in the CON group ($p=0.1$) (Table 4). None of the subjects were receiving enteral nutrition at enrollment, and enteral nutrition was initiated at 18 ± 9 and 17 ± 8 days of age in LOW and CON group, respectively ($p=0.7$).

The incidence of cholestasis at the two study sites was not different when the LOW group was compared to the CON group ($p=1$ at each site). For subjects who received PN for greater than 28 days, the incidence of cholestasis was 30% for the LOW group and 40% for the CON group ($p=0.7$). Moreover, the maximum DB was not statistically significant when the LOW group was compared to the CON group (1.7 ± 1.4 vs. 2.5 ± 2 mg/dL, $p=0.5$) (Figure 2B).

Adverse events occurred infrequently in this study with comparable incidences of hyperglycemia (10% vs. 0%, $p=0.5$) and hypertriglyceridemia (0% vs. 6%, $p=0.4$) in the LOW and CON group, respectively. One CON subject was withdrawn from the study in order to receive intravenous fish oil at 81 days of age. The DB prior to withdrawal was 3.5 mg/dL. The patient was discharged home with PN. There were no deaths in the study.

Discussion

In this pilot study, low dose (approximately 1 g/kg/day) when compared to a higher dose of S-ILE (approximately 3 g/kg/day) was not associated with a change in cholestasis or short-term growth (Tables 2 and 4). However, serum DB rose at a slower rate over the first eight weight weeks and entire study period in the LOW group when compared to the CON group (Table 3). These results are in contrast to a retrospective study by Sanchez *et al.* In this study, a 50% reduction in cholestasis was observed in surgical neonates who received 1 g/kg/d of S-ILE in comparison to a historical cohort. However, it is unclear if these results are due to change in S-ILE dose or clinical practice.¹⁸

Currently in the United States, only one lipid emulsion (20% Intralipid®, Fresenius Kabi, Uppsala, Sweden) is FDA approved. Access to alternative lipid emulsions, such as fish oil or mixed lipid emulsions, is restricted to research and compassionate use protocols.^{9,10,19,20} Because PNALD preventative and therapeutic options are limited, many clinicians have adopted S-ILE dose reduction.^{12,17,18,21,22} Only two other randomized controlled studies have investigated the safety and efficacy of low dose S-ILE in the neonatal population for PNALD prevention.^{7,8} In a study by Rollins *et al.*, 30 neonates with GD who were predicted to require greater than 50% of their calories from PN were randomized to 1 or 3 g/kg/day of S-ILE for no longer than eight weeks. In comparison to the neonates who received the standard dose, neonates who received a reduced dose of S-ILE had a smaller median change in conjugated bilirubin (0 vs. 1.3 mg/dL, $p=0.04$) and total bile acids (2 vs. 13-fold, $p=0.02$). However, in contrast to our study, when the reduced group was compared to the standard group, the median rate of change for conjugated bilirubin was not different (0.02 vs. 0.15 mg/dL/week, $p=0.1$).⁸ It remains unknown if changes in bile acids would be statistically significant in our study.

In a randomized controlled trial by Levit *et al.*⁷ of 136 neonates with a gestational age ≥ 29 weeks, there was no difference in cholestasis, liver function tests, or growth when the S-ILE restricted group was compared to the control group. DB rate of change was not investigated in their study. In comparison to our study, the negative findings they demonstrated may be the result of a lower PNALD incidence in low birth weight neonates (approximately 10% vs. 35%), a shorter PN duration (approximately 19 vs. 40 days), the use of two different S-ILE, and/or a higher glucose delivery rate in the low dose group in comparison to the control group.⁷ In order to compensate for reduced lipid calories, a higher parenteral glucose delivery rate may be required when enteral nutrition is limited. It remains unclear if a high glucose delivery rate may counteract the possible hepatoprotective effect of low dose S-ILE.²³

S-ILE doses less than 1 g/kg/day should be used with caution considering the potential negative impact on growth and risk of an essential fatty acid deficiency and hepatic steatosis, particularly in low birth weight neonates who have limited adipose stores and/or neonates with minimal or no enteral intake.^{8,12,24} Intravenous lipid emulsions provide calories and essential fatty acids, which play a vital role in organogenesis. In the study published by Rollins *et al.*⁸, neonates who received a reduced dose of S-ILE had decreased weight z scores in comparison to controls. Long-term growth and neurodevelopment follow-up for neonates

who have received low dose S-ILE is lacking and needed before this strategy can be widely adopted as part of clinical practice.²⁵ While our study did not monitor for an essential fatty acid deficiency, traditionally defined as a triene/tetrane ratio > 0.2 , this would be unlikely to occur with a dose of 1 g/kg/day of S-ILE.⁸ In a study of neonates with cholestasis who received 1 g/kg of S-ILE twice a week, none of the subjects developed a triene/tetrane ratio > 0.2 . In fact, the initial median (range) triene/tetrane ratio in the lipid restricted group was 0.069 (0.017-0.136). After one month of lipid restriction, the ratio decreased to 0.025 (0.014-0.052). However, neonates may still be at risk for a deficiency in a specific fatty acid.¹²

The increased use of and research on alternative lipid emulsions for PNALD prevention and treatment highlights the on-going controversy about the association of intravenous lipid emulsions and PNALD. Various constituents of S-ILE have been linked to PNALD—high concentrations of phytosterols and omega-6 fatty acids, and insufficient concentrations of omega-3 fatty acids and Vitamin E (α -tocopherol).^{13–15} Intravenous fish oil, which is dosed at 1 g/kg/d, has been associated with improved DB profiles and a possible decrease in transplantation rates and death from liver failure.^{9,10} Fish oil, lacks phytosterols and contains a high concentration of eicosapentaenoic and docosahexaenoic acids (ω -3 fatty acids) and α -tocopherol, an antioxidant that prevents lipid peroxidation and oxidative injury. On the other hand, S-ILE, which is traditionally dosed at 3 g/kg/d, is replete with phytosterols and eicosapentaenoic and docosahexaenoic acid and contains a higher concentrations of omega-6 fatty acids. Also, S-ILE contains γ -tocopherol, which is not as biologically active as α -tocopherol. As a result, it remains controversial if the dose and/or composition of an intravenous fatty acid emulsion is responsible for the development and progression of PNALD.^{7–10}

Normal human phytosterol intake is modest, and as a result, there is minimal phytosterol concentrations in the bloodstream. However, intravenous administration, especially to neonates, provides a large bolus that may overwhelm endogenous protective systems.^{13,26–30} Cell based and animal work demonstrate that phytosterols decrease bile acid transport via the antagonism of the hepatic nuclear receptors farnesoid X and liver X (FXR and LXR).¹³ In contrast, in a different animal model, the addition of α -tocopherol to S-ILE preserved liver function. Moreover, these animals had similar liver function when compared to animals who received fish oil alone and fish oil plus phytosterols.¹⁵ While these studies provide conflicting, yet important information on the hepatic impact of different S-ILE constituents, there has yet to be a study examining the effect of two different doses of S-ILE on phytosterols and immunomodulatory and antioxidant biomarkers.

Limitations of our study include the unmasked design, small sample size, lower than expected PNALD incidence, exclusion of neonates with necrotizing enterocolitis, missing data, and multiple comparisons. It would be challenging to effectively mask the S-ILE dose for this study as it is not routinely mixed in PN solutions at our institutions. However, glucose delivery rates were not different between the two arms despite the unmasked design (Table 4).⁷ Also, to control for S-ILE dose, subjects were recruited shortly after birth. As a result, neonates with necrotizing enterocolitis, who are at high risk for PNALD, were not initially included in this study.¹ Last, because the prediction of which neonates will require

long-term PN is sometimes difficult, 5 patients were excluded from the final analysis as they were weaned from PN by 14 days of age.^{7,8}

Conclusion

In this pilot study, a low dose of S-ILE was not associated with a change in cholestasis or short-term growth in neonates with GD. However, a lower dose of S-ILE was associated with a slower DB increase over time. Considering the morbidity and mortality associated with pediatric PNALD, an appropriately powered study comparing low dose S-ILE to the conventional higher dose of S-ILE is justified.

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Abbreviations

GD	gastrointestinal disorders
PNALD	parenteral nutrition associated liver disease
S-ILE	soybean-based intravenous lipid emulsion
DB	direct bilirubin
PN	parenteral nutrition
ALT	alanine aminotransferase
AST	aspartate aminotransferase

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Clinical Relevancy Statement

Decreasing the incidence and severity of pediatric parenteral nutrition associated liver disease is essential for reducing the morbidity and mortality associated with this disease. Results from this study show that serum direct bilirubin increased at a slower rate in neonates with gastrointestinal disorders who received a lower dose of a soybean-based intravenous lipid emulsion in comparison to a higher dose.

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Figure 1.
Consort diagram.

Figure 2.

Direct bilirubin (DB) profiles for each group for the entire study population (2A) and subjects who received parenteral nutrition > 28 days (2B). The sample size (n) is provided beneath each study week.

Table 1
Baseline Subject Characteristics

Baseline characteristics for the study population. Results are presented as a mean ($\pm$ SD) or percentage (n). DB, direct bilirubin. AST, aspartate aminotransferase. ALT, alanine aminotransferase.

Subject Characteristics	CON (n=16)	LOW (n=20)	p-value
Gestational age (weeks)	36 $\pm$ 2	37 $\pm$ 1	0.6
Birth weight (kg)	2.5 $\pm$ 0.6	2.5 $\pm$ 0.4	0.9
Birth length (cm)	45 $\pm$ 4	45 $\pm$ 3	0.9
Birth head circumference (cm)	33 $\pm$ 4	32 $\pm$ 2	0.3
Male	63 (10)	40 (8)	0.3
Gastrointestinal Diagnosis			0.2
Gastroschisis	75 (12)	75 (15)	
Omphalocele	6 (1)	20 (4)	
Atresia	19 (3)	0	
Meconium Disease	0	5 (1)	
Secondary Gastrointestinal Diagnosis	6 (1)	25 (1)	
Vaginal delivery	38 (6)	50 (10)	0.5
Apgar score < 5 at 5 minutes	6 (1)	10 (2)	1
Maternal Age (years)	23 $\pm$ 6	24 $\pm$ 6	0.6
Maternal Race			1
White	88 (14)	85 (17)	
Black	12 (2)	15 (3)	
Maternal ethnicity—Hispanic	69 (11)	35 (7)	0.09
Baseline DB (mg/dL)	0.45 $\pm$ 0.2	0.55 $\pm$ 0.33	0.3
Baseline AST (IU/L)	52 $\pm$ 66	136 $\pm$ 346	0.3
Baseline ALT (IU/L)	31 $\pm$ 53	115 $\pm$ 42	0.5

Table 2**Study Outcomes**

Results are presented as a mean ($\pm$ SD) or percentage (n). PN, parenteral nutrition. DB, direct bilirubin. AST, aspartate aminotransferase. ALT, alanine aminotransferase.

Outcomes	CON (n=16)	LOW (n=20)	p-value
Primary Outcome - Cholestasis	38 (6)	30 (6)	0.7
Secondary Outcomes			
Weight velocity (g/day), first 28 days	24 $\pm$ 16	18 $\pm$ 8	0.3
PN duration (day)	41 $\pm$ 27	42 $\pm$ 33	0.8
Late onset sepsis	19 (3)	15 (3)	0.3
Secondary Outcomes			
Maximum DB (mg/dL)	1.9 $\pm$ 1.8	1.5 $\pm$ 1.4	0.5
Day of life maximum DB reached	25 $\pm$ 13	27 $\pm$ 14	
Maximum AST (IU/L)	73 $\pm$ 78	90 $\pm$ 80	0.5
Maximum ALT (IU/L)	59 $\pm$ 71	72 $\pm$ 73	0.6
Maximum triglyceride (mg/dL)	137 $\pm$ 113	99 $\pm$ 42	0.2
DB > 1 mg/dL	56 (9)	50 (10)	0.8
Other Variables			
Necrotizing enterocolitis	19 (3)	5 (1)	
Abdominal surgeries	1.9 $\pm$ 0.8	1.9 $\pm$ 0.8	0.7
Length of hospital stay (day)	58 $\pm$ 47	54 $\pm$ 38	0.8
Discharge weight (g)	3.5 $\pm$ 0.7	3.4 $\pm$ 0.9	0.9
Discharge length (cm)	50 $\pm$ 4	51 $\pm$ 4	0.3
Discharge head circumference (cm)	36 $\pm$ 4	35 $\pm$ 2	0.6

Table 3
Rates of Change for Direct Bilirubin and Other Liver Function Tests

Results are presented as a mean ($\pm$ SE). DB, direct bilirubin. AST, aspartate aminotransferase. ALT, alanine aminotransferase. GGT, gamma-glutamyl transferase.

Laboratory Variable	Baseline		Rate of Change to Maximum Value (per week)			
	CON	LOW	p-value	CON	LOW	p-value
DB (mg/dL)	0.4±0.06	0.6±0.08	0.05	0.5±0.09	0.3±0.08	0.2
AST (IU/L)	29±9	90±42	0.2	11±2	-3±10	0.2
ALT (IU/L)	10±8	64±46	0.2	12±2	0.3±8	0.2
Alkaline Phosphatase (IU/L)	147±19	113±10	0.1	38±7	38±6	1
Triglyceride (mg/dL)	70±9	63±6	0.5	13±10	2±1	0.3
	Baseline		Rate of Change (per week)			
DB, Week 4 (mg/dL)	0.5±0.05	0.6±0.07	0.1	0.3±0.06	0.2±0.09	0.6
DB, Week 8 (mg/dL)	0.5±0.06	0.7±0.1	0.05	0.3±0.09	0.07±0.04	0.01
DB Overall (mg/dL)	0.5±0.05	0.7±0.08	0.1	0.2±0.07	0.008±0.03	0.02

Table 4**Rates of Change for Nutritional Variables**

Mixed effects models for growth and parental and enteral nutrition. Results are presented as a mean ($\pm$ SE). GDR, glucose delivery rate. S-ILE, soybean-based intravenous lipid emulsion. PN, parenteral nutrition. *Analysis included birth weight.

Nutritional Variable	Study Week One			Rate of Change (per week)		
	CON	LOW	p-value	CON	LOW	p-value
Weight (kg)*	2.5 $\pm$ 0.15	2.5 $\pm$ 0.09	1	0.17 $\pm$ 0.03	0.12 $\pm$ 0.01	0.1
GDR (mg/kg/min)	12.1 $\pm$ 0.7	13.1 $\pm$ 0.3	0.5	-0.7 $\pm$ 0.4	0.4 $\pm$ 0.3	0.6
Amino Acids (g/kg/day)	3.3 $\pm$ 0.2	3.5 $\pm$ 0.09	0.7	-0.2 $\pm$ 0.1	-0.08 $\pm$ 0.07	0.3
S-ILE (g/kg/day)	2.9 $\pm$ 0.1	1 $\pm$ 0.01	<0.001	-0.2 $\pm$ 0.1	-0.01 $\pm$ 0.005	0.1
PN (kcal/kg/day)	100 $\pm$ 5	88 $\pm$ 2	0.08	-5.4 $\pm$ 3.1	-2.4 $\pm$ 2.4	0.4
Enteral nutrition (kcal/kg/day)	30 $\pm$ 14	6 $\pm$ 13	0.4	16 $\pm$ 7	19 $\pm$ 9	0.8