Influence of Soybean Oil or Non-Soybean Oil Based Lipid Emulsions on Parenteral Nutrition Associated Liver Disease in Late Preterm and Term Infants

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Abstract: *Background*: Total parenteral nutrition (TPN) is a life-saving therapy given to neonates with intestinal failure. However, infants on long-term TPN may experience Parenteral Nutrition-Associated Liver Disease (PNALD). New formulations for lipid emulsions are purportedly better than the traditional soy-based lipid emulsions (SLE). Our primary objective was to determine the prevalence of PNALD in infants who received non-soybean-based lipid emulsions (NSLE) or SLE.

Methods: In this retrospective study, medical records of all infants admitted to a tertiary neonatal intensive care unitfrom 2004 to 2013 were reviewed. Late preterm (34 -36 weeks of gestation) and term infants who were on TPN for more than two weeks were included. Their demographic data and clinical variables were collected.

Results: 208 infants received SLE for more than two weeks. The prevalence rate of PNALD in those who received SLE was 21% while that of those who received the NSLE was 17%. No significant difference was found between the *'Soy'* or *'NonSoy'* subgroups (p = 0.315). Seventy infants received TPN for more than four weeks. The prevalence rate of PNALD in infants who received SLE and NSLE was 35% and 25% respectively. No significant statistical difference was found between the *'Soy'* or *'NonSoy'* subgroups (p = 0.132).

Conclusions: The type of lipid emulsion does not significantly influence the rate of PNALD in late preterm and term infants on long-term TPN.

Keywords: Parenteral Nutrition-Associated Liver Disease, lipid emulsion, fish-oil, soy, soybean, lipid emulsion, cholestasis, neonates, total parenteral nutrition, term infants.

INTRODUCTION

Total parenteral nutrition (TPN) is the administration of a complete and balanced nutrition when normal feeding is impossible, inadequate or hazardous. It is thus a life-saving therapy for infants with intestinal failure by providing optimal nutrition. TPN is a combination of dextrose, amino acids, lipids, electrolytes, vitamins and trace elements. Up to 60% of infants on long-term TPN experience complications of biliary sludge and cholelithiasis [1]. In children, liver dysfunction typically presents as cholestasis or abdominal pseudotumour [1]. The known risk factors of Parenteral Nutrition Associated Liver Disease (PNALD) in the setting of long-term TPN are prematurity, low birth weight, sepsis and surgical conditions such as necrotizing enterocolitis and gastroschisis [2].

The pathophysiology of PNALD is still poorly understood, but it has been postulated that Soy-based lipid emulsions (SLE) are a contributing factor [3]. SLEs are the earliest lipid emulsions developed to provide a source of essential fatty acids, linoleic acid and alpha linoleic acid for parenterally-fed infants [4]. This is to prevent essential fatty acid deficiency in critical stages of development, which manifests as impaired growth, dermatitis, hepatic steatosis, renal toxicity and pulmonary abnormalities.

Other formulations for lipid emulsions have thus been introduced over the past decade to try and reduce the incidence of PNALD. Olive oil-based lipid emulsions (olive oil: soybean oil ratio of 4:1) contain lower levels of polyunsaturated fatty acids (PUFA) than standard SLE. Although the olive oil-based emulsion has a fatty acid profile that is closer to the recommended profile of total lipid supply in TPN, there is limited evidence for its benefit over SLE despite much speculation about its potential in anti-oxidation [4]. It is also not proven to have any significant effect on immune function, such as leukocyte count or acute phase reactant proteins, in a critical care setting [5]. Fish oil-based lipid emulsions (FLE) have been found to be a safe formulation to use in murine models [6] and preterm neonates. Although many studies suggest a potential superiority of FLE over SLE, more definitive studies are needed to ascertain the benefits of FLE and its possible role in PNALD.

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Our primary objective was to determine and compare the prevalence of cholestasis between late preterm and term neonates who were given long-term standard soybean oil-based lipid emulsion, and those who were given non-soy-based lipid emulsions. Secondary outcomes were evaluation of impact of lipid emulsions for >4weeks on PNALD, and Diisopropyl iminodiacetic acid (DISIDA) scans performed to exclude biliary atresia.

METHODS

Infants

The cohort sample included infants who were admitted to a tertiary, neonatal intensive care unit (NICU), from January 2004 to December 2013 at the Children's Hospital at Westmead, Sydney, Australia. Each record was retrieved and reviewed from the NICU database retrospectively. Eligible infants were born at >34 weeks of gestation, who are treated with either SLE or NSLE for more than two weeks. Subgroup analysis of the cohort includes Group A, which consists of infants who required TPN for two to four weeks (14–27 days), while Group B consists of infants who required TPN for more than four weeks (≥28 days).

For each eligible infant, data collected included: gender, gestational age, birth weight, date of admission, date of discharge, duration on TPN, the type of lipid emulsion administered (SLE or NSLE), and peak serum conjugated bilirubin values from liver function tests. DISIDA scan results were also retrieved and checked for the presence of biliary atresia in the respective neonates. Neonates with no nuclear medicine records available were assumed to not have had DISIDA scans done.

In this study, PNALD was defined as cholestasis in the setting of parenteral nutrition, and cholestasis was defined as a serum level of direct bilirubin at ≥35μmol/L. Infants were classified according to the type of intravenous lipid emulsions received. Those who only received soybean-based (Intralipid®20%) or non-soybean (ClinOleic© or SMOF© respectively) based lipid emulsions were classified as *'Soy'* or '*NonSoy*' respectively.

Bilirubin levels were analysed on a VITROS® 5600 Integrated System using colorimetric technique.

Analysis of Data

Descriptive statistics included mean, median, 1st and 3rd quartile ranges, 95% confidence intervals, unpaired two-tailed Student'st-test and chi-squared tests. The distribution of data from each demographic parameter was plotted on a histogram to determine the normality of distribution. Chi-square analysis was used to evaluate the pattern of gender. All other parameters were evaluated with two-tailed t-tests. Results were considered to be statistically significant if the p-value was less than 0.05.

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.

Ethics

This study was performed in accordance with the ethical standards of the Sydney Children's Hospital Network Human Research Ethics Committee and the University of Sydney Human Research Ethics Committee.

RESULTS

A total of 379 infants received TPN for ≥14 days during their NICU admission, of which 208 had gestational age of >34 weeks and were included in the study. Baseline characteristics were similar in both the 'Soy' and 'NonSoy' arms (Table **1**). In this study cohort of 208 patients, there were 138 infants who had TPN for 14-27 days (Group A), while 70 infants required TPN for ≥28 days (Group B). Baseline demographic characteristics were similar inboth the 'Soy' and 'NonSoy' arms in both Group A and B (Table **1**). There was a greater preponderance of females in the Soyarm who received at least four weeks of TPN (Group B) ($p < 0.05$).

In our study cohort 154 patients received SLE for a median duration of 21 days while 54 patients received NSLE for a median duration of 19 days ($p = 0.291$). They stayed in the NICU for a median period of 33 and 29 days respectively ($p = 0.064$). The prevalence of PNALD in infants who received SLE was 21% while that of those who received NSLE was 17% (Table **3**). There were no significant differences between the prevalence rate of PNALD in infants who received more than two weeks of SLE or NSLE ($p = 0.315$).

In our subgroup analyses (Table **2**), there were 100 infants who received SLE for a median duration of 18.5 days and 38 infants who received NSLE for a median duration of 16.5 days in Group A. They stayed in the NICU for a median of 26 and 25 days respectively ($p = 0.321$). 13 out of 100 infants who received SLE had

Table 1: Characteristics of Study Population

Characteristic	Total Population (n = 208)		
	Soy (n = 154)	Non-Soy (n = 54)	p- Value
Sex			
Male	68	24	
Female	86	30	
p-value	0.147	0.414	
Gestational Age, weeks			
Mean	37.6	37.2	0.213
SD	± 1.77	± 1.49	
Birth Weight, grams			
Mean	2881	2823	0.291
SD	± 670	± 540	
Duration on TPN, days			
Median	21	19	0.685
IQR	19	15.25	
Length of NICU stay, days			
Median	33	29	0.064
IQR	30	27.75	

Table 2: Characteristics of Study Population who Received TPN for 2-4 Weeks (Group A) and ≥4 Weeks (Group B)

Characteristic	Group A (n = 138)			Group B (n = 70)		
	Soy (n = 100)	Non-Soy (n = 38)	p- Value	Soy (n = 54)	Non-Soy (n = 16)	p- Value
Sex						
Male	53	16		15	8	
Female	47	22		39	8	
p-value	0.549	0.330		0.001	1.000	
Gestational Age, weeks						
Mean	37.6	37.3	0.281	37.5	37.4	0.499
SD	± 1.68	± 1.52		± 1.94	± 1.45	
Birth Weight, grams						
Mean	2936	2799	0.251	2780	2715	0.961
SD	± 671	± 464		± 662	± 701	
Duration on TPN, days						
Median	18.5	16.5	0.337	41.5	43.5	0.420
IQR	5	4.5		16.25	23.5	
Length of NICU stay, days						
Median	26	25	0.321	57	50	0.166
IQR	13.25	15.75		25.5	16.75	

PNALD while 5 out of 38 who received NSLE had PNALD. No significant differences were found between the prevalence rates of infants who received two to four weeks of SLE or two to four weeks of NSLE (Table **3**) (24% *vs*. 9%; $p = 0.132$).

Table 3: Prevalence of Parenteral Nutrition-Associated Liver Disease (PNALD) in Infants Receiving Long-Term TPN for ≥2 Weeks (Total Population). Subgroup Analysis: Infants Received TPN for 2-4 Weeks (Group A) and ≥4 Weeks (Group B)

	n	Cholestatic Patients	%	p-Value
Total population				
Soy	154	32	21	0.315
NonSoy	54	9	17	
Group A				
Soy	100	13	24	0.406
NonSoy	38	5	9	
Group B				
Soy	54	19	35	0.132
NonSoy	16	4	25	
p-value			0.109	

In Group B, 54 infants received SLE for median duration of 41.5days while 16 infants received NSLE for a median duration of 43.5 days (p = 0.42). They stayed in the NICU for a median period of 57 and 50 days respectively (p = 0.166) (Table **2**). 19 out of 54 infants who received SLE had PNALD while 4 out of 16 who received NSLE had PNALD (Table **3**). No significant differences were found between the prevalence rates of infants who received more than four weeks of SLE or four weeks of NSLE (Table **3**) (35% *vs*. 25%; p = 0.132). As compared with the patients in Group A, there was also no significant difference found in the prevalence of PNALD between the 2 groups (p = 0.109).

Of the 41 patients who had PNALD, 11 out of 32 infants who received SLE and 3 out of 9 infants who received NSLE for more than 2 weeks had DISIDA scans done. None of the DISIDA scans showed signs of biliary atresia.

DISCUSSION

In our cohort, the prevalence rate of PNALD was not significantly influenced by the duration the infants were on TPN – for two to four weeks (Group A) or for more than four weeks (Group B). However, in a recent prospective cohort study involving surgical infants who received prolonged TPN (at least two weeks), there was a significant reduction in the incidence of PNALD with restricted lipid dosing (1g/kg/day), compared to those who received normal lipid dosing (2-3g/kg/day) [7]. It is known that there is a greater risk of PNALD when infants are on TPN for a longer duration [8, 9]. Given that in our Group B sample size is smaller and there is a skew in the gender distribution of the 'Soy' group, the significance of the increase in PNALD prevalence rates between infants in Group A and B may be underestimated, or confounded by other nutritional components like amino acids in the TPN formulations [9].

We also found that the prevalence rate of PNALD was independent of the type of lipid emulsion that the infants received during their admission. However, these results do not support the accumulating evidence in recent years that SLE may contribute to the pathogenesis of PNALD [2]. It has been proposed that SLEs are rich in n-6 PUFA, providing excessive amounts of linoleic acid and α-linoleic acid, which can promote hepatocyte damage and apoptosis *via* pro-inflammatory mechanisms [2, 10]. SLE formulations also contain high amounts of phytosterol (plant-derived steroid alcohols) that may lead to impaired bile drainage and hepato-biliary dysfunction [11]. Nonetheless, our results are consistent with a randomized controlled trial that showed no effect on liver enzymes in premature infants who received either a mixture of soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil (SMOFLipid) lipid emulsions [10]. Another recent double-blind randomized controlled trial involving nine infants also stated that there was no significant difference in the reversal of PNALD at four months between groups who received SLE or NSLE at 1.5 g/kg/day [12] although study numbers were small. It may thus be postulated that the duration that infants are on TPN is a more significant factor than the type of lipid emulsion used during that time.

Our results thus implicate the increasing use of FLE, as it is believed to be rich in n-3 PUFA, which produces eicosanoids that are less inflammatory than that of n-6 PUFA [4]. FLE do not contain phytosterols and have less n-3 PUFA than SLE, which contribute to the development of PNALD. Several case reports have demonstrated that FLE can be used to replace SLE to reverse PNALD in neonates [2]. In a retrospective study of 23 infants with short bowel syndrome treated with TPN who developed cholestasis, PNALD resolution was seen in 16 – either with increased enteral intake or removal of SLE. The infants also received FLEs as supplementation when SLE was withheld, and this was associated with a normalization of total bilirubin levels and improvement in serum hepatic enzymes [13]. However, some of the infants with short bowel syndrome included in the study were premature and had low birth weights. In our study, we did not find any significant differences between the prevalence rates of PNALD between the infants who received long-term SLE or NSLE (including FLE), and this may be largely due to the fact that our inclusion criteria was for late preterm and term patients (gestational age >34 weeks), hence heavier birth weights. Although there is uncertainty in the exactpathophysiology of PNALD, we know that immature liver function and short bowel syndromes arestrong predisposing factors [14, 15]. The inflammation, secretion of gut hormones and extent of bowel loss associated with short bowel syndrome, as well as the prematurity of the infants in other studies may be a possible confounding factor in other studies that show a benefit of substituting SLE with FLE. Furthermore, there are also concerns whether FLE contain sufficient essential fatty acids to prevent nutritional deficiency because FLE only provide the downstream mediators [8]. Therefore, the benefits of using FLE need to be further elucidated.

Cholescintigraphy is an expensive and invasive procedure. Our results showed that the rates of infants who had DISIDA scans to rule out biliary atresia were comparable between the patient groups who received SLE or NSLE, hence using different lipid emulsions did not contribute to a reduction in the need for an invasive procedure in infants or in the prevention of hepatobiliary disease. Nonetheless, this is based on a fairly limited number of DISIDA scans performed over the last ten years. PNALD is a multifactorial disease entity and other factors such as inflammation and sepsis in the small bowel can contribute to the severity of cholestasis. The level of inflammatory mediators [16] may be influenced by other treatment factors as well, such as the use of ursodeoxycholic acid [17] or antibiotics for management of sepsis.

Retrospective design and a relatively small cohort were limitations of this study.

In conclusion, our study suggests that there is no difference in the effect of using SLE or NSLE on the outcome of late preterm and term infants in relation to cholestasis and PNALD. The lack of an observed beneficial effect in infants who received NSLE in this study paves the way for further objective trials to determine the use of more expensive lipid emulsions in this group of infants on TPN.

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REFERENCES

[1] Lee V. Liver Dysfunction Associated with Parenteral Nutrition: What Are the Options? Practical Gastroenterology 2006; [cited 2013 May 14]. Available from:http://www.medicine.virginia.edu/clinical/departments/medicine/divisions/digestive-health/nutrition-support-team/nutrition-articles/LeeArticle.pdf

[2] Rangel SJ, Calkins CM, Cowles RA, *et al*. Parenteral nutrition-associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. J Pediatr Surg 2012; 47(1): 225-40. http://dx.doi.org/10.1016/j.jpedsurg.2011.10.007

[3] Colomb V, Jobert-Giraud A, Lacaille F, Goulet O, Fournet JC, Ricour C. Role of lipid emulsions in cholestasis associated with long-term parenteral nutrition in children. JPEN J Parenter Enteral Nutr 2000; 24: 345-50. http://dx.doi.org/10.1177/0148607100024006345

[4] Deshpande G, Simmer K. Lipids for parenteral nutrition in neonates. Curr Opin Clin Nutr Metab Care 2011; 14: 145-50. http://dx.doi.org/10.1097/MCO.0b013e3283434562

[5] Mateu-de Antonio J, Grau S, Luque S, Marin-Casino M, Albert I, Ribes E. Comparative effects of olive oil-based and soyabean oil-based emulsions on infection rate and leucocyte count in critically ill patients receiving parenteral nutrition. Br J Nutr 2008; 99: 846-54. http://dx.doi.org/10.1017/S0007114507837433

[6] Kalish BT, Le HD, Gura KM, Bistrian BR, Puder M. A metabolomic analysis of two intravenous lipid emulsions in a murine model. PLoS One 2013; 8: e59653. http://dx.doi.org/10.1371/journal.pone.0059653

[7] 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: 573-8. http://dx.doi.org/10.1016/j.jpedsurg.2012.08.016

[8] Chang MI, Puder M, Gura KM. The use of fish oil lipid emulsion in the treatment of intestinal failure associated liver disease (IFALD). Nutrients 2012; 4: 1828-50. http://dx.doi.org/10.3390/nu4121828

[9] Koseesirikul P, Chotinaruemol S, Ukarapol N. Incidence and risk factors of parenteral nutrition-associated liver disease in newborn infants. Pediatr Int 2012; 54: 434-6. http://dx.doi.org/10.1111/j.1442-200X.2012.03627.x

[10] Tomsits E, Pataki M, Tolgyesi A, Fekete G, Rischak K, Szollar L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial- in premature infants requiring parenteral nutrition. J Pediatr Gastroenterol Nutr 2010; 51: 514-21. http://dx.doi.org/10.1097/MPG.0b013e3181de210c

[11] Clayton PT, Whitfield P, Iyer K. The role of phytosterols in the pathogenesis of liver complications of pediatric parenteral nutrition. Nutrition 1998; 14: 158-64. http://dx.doi.org/10.1016/S0899-9007(97)00233-5

[12] Lam HS, Tam YH, Poon TC, *et al*. A double-blind randomised controlled trial of fish oil-based *vs.* soy-based lipid preparations in the treatment of infants with parenteral nutrition-associated cholestasis. Neonatology 2014; 105: 290-6. http://dx.doi.org/10.1159/000358267

[13] Rollins MD, Scaife ER, Jackson WD, Meyers RL, Mulroy CW, Book LS. Elimination of soybean lipid emulsion in parenteral nutrition and supplementation with enteral fish oil improve cholestasis in infants with short bowel syndrome. Nutr Clin Pract 2010; 25: 199-204. http://dx.doi.org/10.1177/0884533610361477

[14] Robinson DT, Ehrenkranz RA. Parenteral nutrition-associated cholestasis in small for gestational age infants. J Pediatr 2008; 152: 59-62. http://dx.doi.org/10.1016/j.jpeds.2007.06.002

[15] Nandivada P, Carlson SJ, Cowan E, Chang MI, Gura KM, Puder M. Role of parenteral lipid emulsions in the preterm infant. Early Hum Dev 2013; 89(Suppl 2): S45-9. http://dx.doi.org/10.1016/j.earlhumdev.2013.08.005

[16] Kalish BT, Le HD, Fitzgerald JM, *et al*. Intravenous fish oil lipid emulsion promotes a shift toward anti-inflammatory proresolving lipid mediators. Amjphysiol 2013; 305: G818-28. http://dx.doi.org/10.1152/ajpgi.00106.2013

[17] Thibault M, McMahon J, Faubert G, *et al*. Parenteral nutrition-associated liver disease: a retrospective study of ursodeoxycholic Acid use in neonates. J Pediatr Pharmacolther 2014; 19: 42-8. http://dx.doi.org/10.5863/1551-6776-19.1.42

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