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The Effectiveness of Smoflipid on Liver Function in Pediatric Patients with Intestinal Failure Related Parenteral Nutrition Associated Liver Disease (PNALD)

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Abstract

*Background:*Parenteral nutrition (PN) is a treatment that supplies one's nutrition and hydration needs intravenously. Intravenous soybean lipid emulsions have been associated with Parenteral Nutrition Associated Liver Disease (PNALD), due to its high phytosterol content and high n-6:n-3 ratio and its propensity to mitigate inflammatory eicosanoid pathways. Composed of soybean oil, medium chain fatty acids, olive oil, and fish oil, Smoflipid may ameliorate PNALD and mitigate anti-inflammatory eicosanoid pathways.

Objective: To examine the effectiveness of Smoflipid on improving liver function and bilirubin levels on home PN-dependent children with intestinal failure related PNALD.

Design: A prospective electronic medical record review was conducted from 2016-2018 at Loma Linda University Children's Hospital (LLUCH).

Participants: Charts of thirteen outpatient children (8.1±4.2 years, 6 females and 7 males) with intestinal failure who either have completed six-months of Smoflipid or are currently taking Smoflipid.

Main outcomes: Preventing or reducing the severity of PNALD.

Secondary outcomes: Sustaining growth, reducing TPN infection rates and measuring Smoflipid tolerance by assessing essential fatty acid status, fasting glucose levels, hemoglobin A1C, total cholesterol, and serum triglycerides.

Statistics: A Mixed Model was used to account missing values and measure changes in continuous variables. Values were summarized by calculating the mean and standard deviation, before and after Smoflipid treatment.

Results: Although there was a decreasing trend in ALT (N=11, 23.2% after six-months) and AST (N=11, 8.3% after six-months), Smoflipid did not have a statistical significant impact on ALT,

AST, and total bilirubin. There was a significant impact on central line infection rates (n= 5, p=0.032) and hemoglobin A1C (n=3, p=0.001).

Conclusion: Smoflipid may yield biochemical effects in reducing elevated liver enzymes associated with PNALD and enhance the quality of life by improving liver function, sustaining growth, and reducing infection rates, and hemoglobin A1C. Smoflipid may be a beneficial alternative to the standard soybean-based lipid emulsion.

Introduction

Intestinal failure (IF) is a medical condition characterized by the inability of the gastrointestinal (GI) tract to absorb all of the nutrition and fluids needed for normal physiologic function, growth, and/or development.[1] The causes of IF are many, including short bowel syndrome, gastroschisis, congenital intestinal abnormalities, and trauma.[2] Until the 1960's and 1970's, most patients with intestinal failure died because there was no means to provide patients with appropriate nutrition and hydration.[3] The dual inventions of the central venous catheter and the parenteral nutrition dramatically changed the long-term outlook for patient with IF.[4] Parenteral nutrition (PN) is a medical treatment in which 100% of a patient's nutrition and hydration needs can be provided by daily infusion of a customized intravenous solution. The solution generally includes pharmaceutical-grade carbohydrates, proteins, fats, micronutrients and water that are required for normal physiologic function and growth.[3] The almost simultaneous production of long term indwelling central venous catheter, such as the Hickmann and Broviac catheters, afforded the infusion of parenteral nutrition.[3]

Parenteral nutrition is frequently employed in pediatric and adult care in both, acute and long-term settings. To many, total parenteral nutrition (TPN) is an alternative prolonged hospitalization.[5-6] More specifically, within the pediatric setting, PN is utilized in intestinal disorders, such as intestinal failure and Short Bowel Syndrome.[7] While some children are capable of oral intake, PN may be necessary to supplement the diet due to the intestine's impaired ability to absorb nutrients from food.[8]

A typical PN formula is composed of dextrose, amino acids and lipid emulsions.[1] Lipid emulsions are "biologically vital" because they serve as a high-energy supply, deliver essential fatty acids (EFA) that can not be endogenously synthesized, and protect against high glucose

infusion rates.[7] A high glucose infusion rate may lead to complications such as hyperglycemia and hepatic steatosis.[7]The main component of PN lipid emulsions is soybean oil. In the United States, pure soybean oil lipid emulsions (*Lyposyn III* and *Intralipid*) are the dominant fat source in PN.[5] Soybean oil is abundant in two essential fatty acids (EFA), linoleic acid (LA) and alpha linolenic acid (ALA), and has been effective in preventing EFA deficiencies.[8] Despite this success, there are some concerns with both the high phytosterol content and the n-6:n-3 ratio of this emulsion.[9]

One concern pertaining to the use of soybean-based lipid emulsion in PN is attributed to its high phytosterol content. Phytosterols are plant-based and biologically similar to cholesterol. However, the human body cannot metabolize phytosterols.[10] Through enteral nutrition, the intestine only absorbs 5% of phytosterols.[10] However, administration via PN enables 100% uptake of phytosterol into circulation. This can accumulate in the liver and bile, which could ultimately lead to phytosterol-mediated cholestasis and liver injury.[10-11]

Another concern involves the high proportion of n-6:n-3 ratio and its capacity to induce inflammation and hepatotoxicity.[5] LA is part of the n-6 fatty acid (FA) family that are proinflammatory eicosanoid precursors of prostaglandin series-2 and leukotrienes series-4.[12-13] Conversely, ALA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) belong to the n-3 FA family. These fatty acids are anti-inflammatory eicosanoid precursors for the prostaglandin series-3, leukotriene series-5, resolvins, protectins and maresins.[12-13] Research proposes that diets higher in n-6 (proinflammatory), in relation to n-3 (anti-inflammatory), correlate with higher proinflammatory markers in serum levels and enhances thrombin-mediated platelet aggregation.[14-15] Thus, soybean oil-based emulsions raise a concern for its use in PN because of its high n-6 content and its propensity to mitigate proinflammatory pathways. In

addition, recent findings suggest that high amounts of n-6 FA instigate lipid peroxidation.[16]This volatile reaction results in the production of reactive oxygen species (ROS) and additional pro-inflammatory markers (cytokines).[16] In all, high phytosterols and high n:6-n:3 ratios in the soybean-based lipid emulsion can promote inflammatory states and damage vital organs and tissues.

The liver is highly vulnerable to lipid peroxidation. Long-term parenteral feedings can lead to severe complications such as Parenteral Nutrition Associated Liver Disease (PNALD).[16-17] PNALD is an umbrella term for three types of hepatobiliary disorders associated with PN: steatosis, cholestasis and gallbladder stasis.[16-17] Steatosis is identified by mild to moderate levels of serum aminotransferase levels with less pronounced elevations of serum alkaline phosphatase and bilirubin concentrations.[17] Cholestasis refers to an impaired secretion of bile or a biliary obstruction, as evidenced by elevated serum concentrations of alkaline phosphatase, aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and conjugated bilirubin concentrations.[17] Lastly, gallbladder stasis results from lack of oral intake. Decreased release of cholecystokinin (CCK) impairs bile flow and contraction of the gallbladder which results in biliary sludge and gallstones.[17]Thus, PNALD is detrimental because steatosis, cholestasis and gallbladder sludge may lead to fibrosis, cirrhosis and liver failure.[6]PN-dependent children and infants may be more susceptible to liver damage due to age-related hepatic immaturity.[18-19] Treatment options for these conditions are limited and individuals with a weak immunity are highly vulnerable to mortality.[18]

Smoflipid is a balanced lipid profile composed of 30% soybean oil (n-6), 30% medium chain fatty acids, 25% olive oil and 15% fish oil (n-3, EPA and DHA).[20] To address PNALD, Smoflipid was designed to lower the n:6-n-3 ratio and phytosterol content.[9]In doing so, this may

reduce lipid peroxidation and prevent further damage to the liver. Compared to the standard soybean lipid emulsion, Smoflipid contains less phytosterol (~50 mg/L) and more α-tocopherol (~200 mg/L).[5] The previous soybean lipid emulsion had a 7:1 n-6:n-3 ratio.[16] As Smoflipid yields a n-6:n-3 ratio of 2.5:1, this lowers the ratio and improves the overall n-6:n-3 ratio.[20-21] A higher n-3 fatty acids content facilitates in mitigating anti-inflammatory eicosanoid pathways.[8] An increasing body of evidence from Fell et al.,[5] Calder et al.[16], Saayman et al.,[18] Rayyan et al.,[19] Canada et al.,[20] Tomsits et al.,[21] and Goulet et al.[22] support the use of Smoflipid in preventing or reducing the severity of PNALD.[5,16,18-22] Short-term trials suggest that Smoflipid has been deemed safe and well-tolerated in preterm infants.[20] Results from another short-term randomized clinical control trial exhibited improved liver function (bilirubin and γ-glutamyl transferase) with Smoflipid, compared to the standard soybean lipid emulsion.[21-22] Another small retrospective cohort study examined children who developed PNALD from a soybean lipid emulsion and were treated with Smoflipid.[18] In 5 out of the 8 children, results exhibited improvements in cholestasis.[17] Thus, the usage of Smoflipid in preventing PNALD has been shown to be favorable in early clinical trials. In addition to the possible protective effects on the liver, other areas of interest include evaluating the effects of Smoflipid on sustaining growth, reducing TPN central line infection rates, supplying essential fatty acid requirements and overall tolerance through monitoring lab values of serum triglycerides, total cholesterol, fasting glucose and hemoglobin A1C. As Smoflipid is a new treatment, it may be a beneficial alternative to the standard soybean lipid emulsion in pediatric patients with intestinal failure related PNALD.

The purpose of this prospective observational graduate student research study was to examine the effectiveness of Smoflipid on improving liver enzymes (AST, ALT) and total bilirubin levels on home TPN-dependent pediatric patients with intestinal failure related

parenteral nutrition associated liver disease (PNALD). Secondary outcomes examined Smoflipid and its effect on sustaining growth, reducing TPN central line infection rates and overall tolerance. Tolerance of Smoflipid was monitored by assessing essential fatty acid panel (with specific focus on the triene:tetraene ratio), glucose levels (Fasting Glucose and Hemoglobin A1C) and lipid panel (total cholesterol and triglycerides levels). These values assisted in determining appropriate dosage for creating a standard protocol for Smoflipid.

Methods

This research study consisted of six female and seven male outpatient children (n=13) with a mean age of 8.1±4.2 years. Age ranged from six-months to seventeen years of age.To be included in the study, participants must have either have finished 6 months of Smoflipid or are currently taking Smoflipid, be pediatric patients from 6 months to 21 years of age with intestinal failure, receiving home parenteral nutrition (PN) or total parenteral nutrition (TPN) and followed by Pediatric TPN Clinic. There was no exclusion criteria.

The Institutional Review Board of Loma Linda University approved all methods and procedures. Risks of this study included a possible breach of confidentiality. Although patients may not personally benefit from this study, their participation may help practitioners see if Smoflipid improves intestinal failure and assist in establishing a standard protocol for Loma Linda University Children's Hospital.

An electronic medical record (EMR) review was conducted on patients who currently received Smoflipid emulsion or have finished six-months of Smoflipid from 2016 to 2018. EMR information was accessed via one computer at Loma Linda University Children's Hospital through the electronic record program titled Loma Linda Electronic Access Portal (LLEAP). Routine lab values for patients were completed monthly for all patients on TPN. Lab values

were examined three times: before the start of Smoflipid, at three-months and again at the end of six-months of Smoflipid. Hemoglobin A1C, triene-tetraene ratios and serum triglyceride levels were routinely measured for patients. Hemoglobin A1C was measured one-week prior to Smoflipid initiation and every three-months after. Essential fatty acid status was assessed by the triene-tetraene ratio and these values were obtained before initiation of Smoflipid and every six-months after initiation. Blood glucose measurements were monitored closely when undergoing Smoflipid infusions.

Data obtained from the electronic chart review consisted of age, gender, anthropometrics (weight, length/height, BMI), primary diagnosis/cause of TPN dependency, length of time on Smoflipid and % of total calories provided by TPN. Lab values assessed included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, hemoglobin A1C, fasting blood glucose, total cholesterol, serum triglycerides and essential fatty acid panel with specific focus on the triene:tetraene ratio.

A prospective chart review was conducted at the Loma Linda University Children's Hospital. Student investigators obtained access to LLEAP and were instructed on which patients to include in the study. Patient charts were divided equally among student investigators and follow-up values were conducted by the original assigned student investigator.

To ensure reliability of the data collection process, an inter-rater reliability system was utilized. One student investigator recorded data from their assigned patient charts. Another student investigator also collected data from the same assigned patients. The recorded data was compared. This ensured a level of consensus among raters.

Upon entering the study, a unique study number was assigned to each patient in alignment with a coding system to help organize patient information and protect personal

information. The master code key linking the study ID to participant names was only accessible to the primary investigator and co-investigators. This master code key was kept electronically on a single password protected University desktop computer inside a locked office within a locked building within Dr. Khiet Ngo's office in Room A1110A at Loma Linda University Medical Center Coleman Pavilion. In the event there was loss of electronic data, a hardcopy of this code was maintained in the same secure office. Data will be kept for 10 years after completion of the study in the event there are questions raised after the results are published in which having original data will help provide the answer. All data was recorded on an excel spreadsheet and other notes was made in a computer file. Lab values were examined three times: before the start of Smoflipid, at the three-month of Smoflipid and at the end of six-months of Smoflipid. Data collection was composed of age, gender, primary diagnosis/cause of TPN dependency, anthropometrics (i.e. weight, length/height and BMI), lab values (i.e. liver enzymes (ALT/AST), total bilirubin, lipid panel (total cholesterol and triglycerides), essential fatty acid panel (triene:tetraene), hemoglobin A1C, and fasting glucose), number of days on Smoflipid,% dextrose and % protein provided by TPN, total grams/day and grams/kg of protein and carbohydrates provided by TPN, glucose Infusion Rate, Smoflipid cycle (hr/day), current Smoflipid rate (ml/hr) and maximum Smoflipid rate (ml/kg/hr), number of hospitalizations, and number of TPN central line infections.

A Mixed Model was conducted to measure the changes in values, before and after treatment. Data consists of quantitative variables. These were classified as continuous and summarized by calculating the mean and standard deviation for both pre-measurement (one-month prior the start of Smoflipid and post-measurement (after three-months and six-months of

Smoflipid). As there were random missing data values, The Mixed Model was used to handle these missing data values and provide unbiased estimates of the means.

Results

Table 1. Mean (SD) of Liver Enzymes (ALT, AST) and Total Bilirubin Levels During the Six-Months on Smoflipid Emulsion (N=13).

	Pre-Smoflipid			Month 3			Month 6			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p-value
ALT (U/L)	13	108.2	73	13	79.2	38.1	11	83.2	43.4	
Mean Difference		Reference			-29.1			-25.1		0.247
Percent Change		Reference			-26.9%			-23.2%		
AST (U/L)	13	79.4	46.6	13	70.6	40.0	11	71.1	32.8	
Mean Difference		Reference			-8.8			-8.3		0.741
Percent Change		Reference			-11.0%			-10.4%		
Total Bilirubin (mg/dL)	13	0.85	0.87	13	0.88	0.90	11	0.92	1.01	
Mean Difference		Reference			0.0			0.1		0.386
Percent Change		Reference			3.6%			8.3%		
SD: Standard Deviation ALT: Alanine Aminotransferase AST: Aspartate Aminotransferase										

Results indicated that Smoflipid led to an overall decrease in alanine transaminase (ALT) and aspartate transaminase (AST) values, after the three-month and six-month period. From the initiation of Smoflipid emulsion, there was a 26.9% decrease (108.2 U/L to 79.2 U/L) in ALT at three-months and a 23.2% decrease (108.2 U/L to 83.2U/L) at six-months (Table 1) (p=0.247). In terms of AST values, there was an 8.8% decrease (79.4 U/L to 70.6 U/L) at three-months and an 8.3% decrease (79.4 U/L to 71.1 U/L) at six-months (Table 1) (p=0.741). With respect to total bilirubin, there was a slight increase (0.85 mg/dL to 0.88mg/dL) of 3.6% at three-months and 8.3% increase (0.85 mg/dL to 0.92 mg/dL) at six months (Table 1) (p=0.386). Over the past six-months, Smoflipid did not have a statistical significant impact on ALT, AST and total bilirubin.

Table 2. Mean (SD) of BMI, Central Line Infection Rates, Hemoglobin A1C, Total Cholesterol, Glucose and Triglycerides During the Six-Months on Smoflipid Emulsion (N=13).

	Pre-Smoflipid			Month 3			Month 6			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	p-value
BMI (kg/m2)	13	17.5	2.4	13	17.3	1.4	11	17.9	1.6	
Mean Difference		Reference			-0.2			0.4		0.075
Percent Change		Reference			-1.0%			2.2%%		
Infections (# of occurrences)	5	1.2	0.5	10	0.2	0.5	5	0.2	0.3	**0.032***
Mean Difference		Reference			-1.0			-1.0		
Percent Change		Reference			-80.6%			-80.7%		
Glucose, Fasting (mg/dL	13	90.4	18.5	13	80.8	16.7	11	95.1	24.5	
Mean Difference		Reference			-9.5			4.8		0.171
Percent Change		Reference			-10.6%			5.3%		
Hemoglobin A1C (%)	8	4.72	0.65	6	4.6	0.23	3	3.9	0.03	
Mean Difference		Reference			-0.1			-0.8		**0.001***
Percent Change		Reference			-2.6%			-17.3%		
Total Cholesterol (mg/dL)	13	114.2	29.3	13	114.5	34.0	11	117.4	40.1	
Mean Difference		Reference			0.2			3.1		0.906
Percent Change		Reference			0.2%			2.7%		
Triglycerides (mg/dL)	13	74.8	34.1	13	66.4	31.4	11	61.9	29.5	
Mean Difference		Reference			-8.5			-13		0.104
Percent Change		Reference			-11.3%			-17.3%		
* indicates significance at an alpha of 0.05										
SD: Standard Deviation BMI: Body Mass Index										

As illustrated in Table 2, results showed that Smoflipid did not yield a statistical significant result overtime with respect to reducing BMI (p = 0.075), fasting glucose (p=0.171), total cholesterol (p = 0.906), and triglycerides (p = 0.104). Smoflipid yielded a statistically significant impact on TPN central line infection rates for five participants in the study (p=0.032), and exhibited a decrease in TPN central line infection rates of 80.7%. Regarding hemoglobin A1C, Smoflipid yielded a decrease of 17.3% (p=0.001), at the six month period in three participants. A 2.6% decrease was observed during the three-month period in six participants. Lastly, in regards to measuring tolerance of Smoflipid by monitoring essential fatty acid deficiencies through examining triene-tetraene ratios, values remained within the normal limits

of 0.013 to 0.050. Mean average values of the triene:tetraene ratio values were measured at 0.03 at three-months in ten participants and 0.04 in five participants at six-months (p=0.001) (Figure 1). There were not any indications of essential fatty acid deficiencies among participants in this study. Sample size of secondary outcomes fluctuated with each time measurement, throughout the study, due to the availability of data.

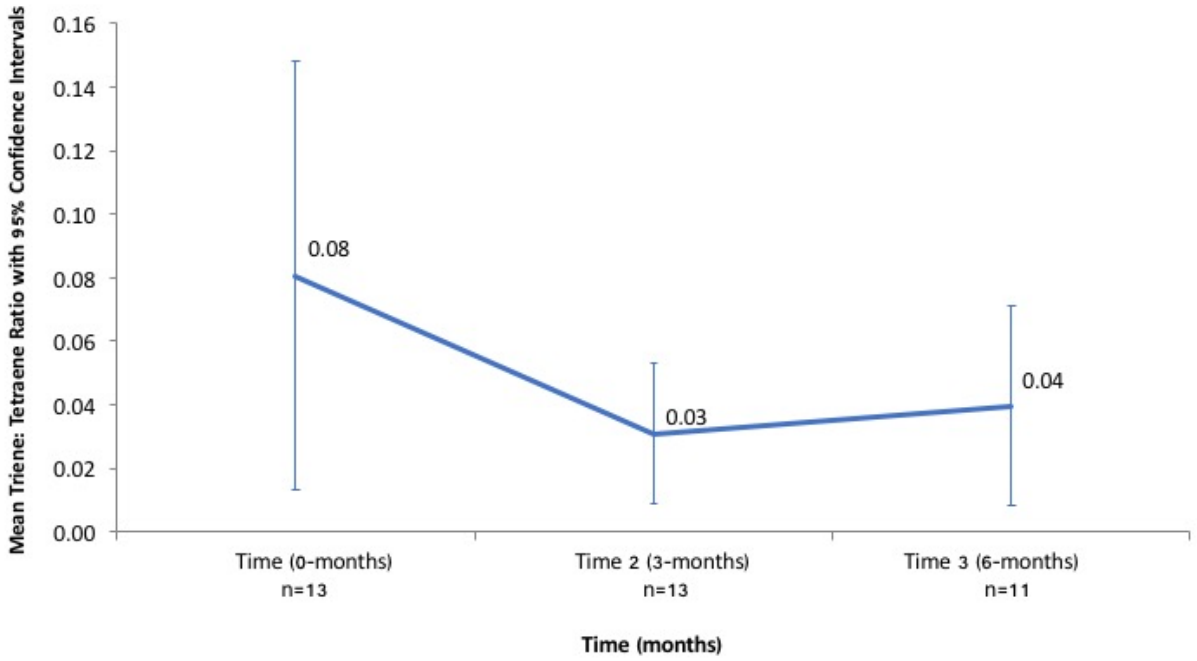

Figure 1. Mean Triene:Tetraene Ratio (Normal Limit Ranges: 0.013-0.050) During Six-Months of Smoflipid Emulsion.

Discussion

Smoflipid emulsion is a new treatment that may be a beneficial alternative to the standard soybean-based lipid emulsion. The primary outcome of this study examined the effectiveness of Smoflipid on improving liver enzymes (AST and ALT) and total bilirubin levels on home-dependent pediatric patients with intestinal failure related parenteral nutrition associated liver

disease (PNALD). In this study, Smoflipid was well-tolerated among most of the pediatric patients. Consistent with the present findings, Goulet et al.[22] also reported that Smoflipid was well-tolerated and safe among pediatric patients receiving home TPN. In regards to liver enzymes, there was not any significant impact found in the reduction of AST and ALT. Research literature reports inconsistent results with Smoflipid and its effect on reducing liver enzymes.[22,23] In a randomized, controlled, double-blind, multicenter study among adult patient patients with intestinal failure, Klek et al.[23] reported that the use of Smoflipid had significantly decreased the ALT and AST levels after the treatment period. Conversely, a study by Goulet et al.,[22] conducted on the pediatric population, did not observe any significant difference in the reduction of liver enzymes. It is important to note, in our study, there was a decreasing trend in AST and ALT values. After the six-month of Smoflipid therapy, AST and ALT values were lower than their respective values at baseline levels. Thus, this suggests that Smoflipid may yield potential clinical biochemical effects in reducing elevated liver enzymes associated with PNALD.

Furthermore, Calkins, et al.[24] examined the effects of replacing intravenous (IV) soybean oil with fish oil, with the goal of ameliorating cholestasis. After six months, there were reductions in direct and total bilirubin.[24] As this study used pure fish oil, it is highly plausible that fish oil may yield different effects compared to mixed emulsion like Smoflipid.[24] Results on using a mixed lipid emulsion in treating and preventing intestinal failure associated liver disease (IFALD) remains conflicting. Furthermore, a randomized control trial by Diamond et al.[25] compared patients on Smoflipid and Intralipid. Results demonstrated that Smoflipid was linked with decreasing serum bilirubin.[25] Inconsistent with the findings of current literature of Smoflipid decreasing bilirubin levels, our study did not exhibited any reduction in bilirubin. Overall, there was a slight increase in total bilirubin trends among pediatric patients on

Smoflipid. We suggest that this slight increase in bilirubin may be attributed to the observational nature of the study and the small and heterogeneous nature of the sample size.

Secondary outcomes examined Smoflipid and its effect on sustaining growth, reducing TPN central line infection rates and overall tolerance through monitoring essential fatty acid panel (with specific focus on the triene:tetraene ratio), glucose levels (Fasting Glucose and Hemoglobin A1C) and lipid panel (total cholesterol and triglycerides levels). In our study, Smoflipid was tolerated well among the pediatric patients without any side effects, and long-term use showed to decrease infection rates and hemoglobin A1C, which was beneficial for the patients who are on Smoflipid. Other studies such as Goulet et al.,[22] Diamond et al.,[24] and Calkins et al.[25] have not shown decreased hemoglobin A1C in pediatric patients. However, a review by Montori et al,[26] demonstrated that the addition of fish oil in PN formula lowered triglycerides and LDL levels, which in turn improved insulin sensitivity. Recent research by Riserus et al.[27] suggested elevated lipid levels in the blood may block insulin signaling cycles to the cell. Thus, lipid reduction may improve glucose utilization.[27] A significant impact in reduction in hemoglobin A1C was an unexpected finding. However, it is crucial to take in account that this is exploratory data. Therefore, clinical decisions cannot be made at this time on the effects of Smoflipid on hemoglobin A1C. A systematic review and meta-analysis by Manzanares et al.[28] examined infection rates in five randomized controlled clinical trials, within the critically-ill population, on the use of fish oil-based lipid emulsions in PN formulas.[28] All five trials found the fish oil based lipid emulsions did not exhibit any effect on mortality and had a statistically significant effect on the reduction of infection rates.[28] However, the impact of fish-oil based lipid emulsions in reducing infection rates remains inconclusive. In other randomized controlled trials, assessed by Manzanares et al.,[28] Smoflipid had the same effect on infection

rates as other lipid emulsions. This generates new questions and sparks future areas of research with the effects of Smoflipid on infection rates and hemoglobin A1C. Furthermore, consistent with other findings, Smoflipid did not cause any complications in regards to growth, total cholesterol, triglycerides and essential fatty acid status. Parallel to the findings of Pichler, J., et al.,[29] this study compared a new IV lipid emulsion (Lipofundin: MCT and soybean oil) and a mixed IV lipid emulsion (Smoflipid). There were no differences in respect to infection rates, total cholesterol, and serum triglycerides, between the the Lipofundin and Smoflipid groups. No side effects were displayed in the children on Smoflipid or Lipofundin, but a significant nutritional improvement weight gain was reported in both groups.[28] Although it remains unclear as to why there were not any differences found, regarding infection rates, total cholesterol, and serum triglycerides, when comparing soybean-based and fish oil-based lipid emulsions, this demonstrates that a mixed lipid emulsions, like Smoflipid, can potentially be safe, well-tolerated and meet the nutrient needs within the parenteral nutrition dependent population. The anti-inflammatory nature of the reduced phytosterol content, improved omega-6 to omega-3 ratio and increased alpha-tocopherol, supports the advantages of using a fish oil-based lipid emulsion over the standard soybean-based lipid emulsion.

Complications during the study included one twelve year-old participant with severe hyperglycemia, upon the start of Smoflipid. Although this phenomenon is rare, there has been incidences in preterm infants where hyperglycemia was a result of the introduction of PN formula. It is speculated that this rise in serum glucose level is due to the increase in FFAs as a result of lowering the amount of glucose being utilized peripherally or decreasing insulin suppression of glucose production from the liver.[26] One common cause of hyperglycemia involve high dextrose infusion rates. It is common for rebound hypoglycemia to transpire after

an abruptly stopping parenteral nutrition.[30] To prevent glucose and insulin abnormalities, the cycle of parenteral nutrition is advanced over two hours and subsequently tapered off over two hours.[30] To monitor blood glucose levels, these values are checked at peak infusion rate and again post 30-minutes after stopping parenteral nutrition.[30] In the one patient that experienced severe hyperglycemia, extensive measures were taken to eliminate other confounding factors that may be eliciting abnormal blood glucose levels. Home diet, medications, glucose infusion rate, time of when glucose levels were assessed and overall nutrition support regimen remained the same. The only modification to the program was switching from Intralipid to Smoflipid. One possible theory on the correlation of hyperglycemia and initiation of Smoflipid pertains to the interplay of the gut microbiome on parenteral nutrition dependent patients. Very few studies exist on examining the intestinal microbiota in TPN-dependent pediatric patients with short bowel syndrome (SBS).[31,32,33] Lila et al.[31] and Cahova et al.[32] examined the gut microbiome and the ramifications of parenteral nutrition in initiating gut dysbiosis, impaired gut barrier function and inflammation. Lilja et al.[31] was one of the first human studies exploring this role and reported that pediatric patients with SBS have "microbial dysbiosis" which lowers the diversity bacterial diversity in their intestinal microbiome. This may be the culprit in mitigating pro-inflammatory bowel diseases.[31] A review by Cahova et al.[32] reports that there is a complex and multifaceted interplay of how parenteral nutrition may detrimentally elicit dysbiosis, which could also be one of the precipitating factors in the development of PNALD.[32] Interestingly, in an in-vitro study on neonatal pigs conducted by Lavalle et al.,[33] they compared the microbiome response of Smoflipid and the standard soybean-based lipid emulsion. Findings reported that different lipid emulsions had various effects on gut microbiota diversity and gut barrier function.[33] Although the exact mechanism has not been identified, long-chain omega-3 fatty

acids, from Smoflipid, facilitated in improving the bacterial microbiota interactions on the intestinal mucosa.[33] Unfortunately, to date, there is not any research examining how glucose metabolism is affected by these mixed lipid emulsions. However, it is plausible that the gut microbiome may play a role in glucose and insulin metabolism and homeostasis. More research is needed on the interplay between the gut microbiome on metabolism, in parenteral nutrition dependent patients.

Another complication involved a five-year old participant who was presented with epistaxis at the end of the six-months and was subsequently discontinued from Smoflipid therapy. One explanation of epistaxis includes the omega-3 fatty acid component of fish oil in Smoflipid. Omega-3 fatty acids have lower prothrombotic properties and are often been employed in preventative measures for coronary heart disease.[34] However, their propensity to decrease platelet aggregation raises concern for prolonged bleeding times and increased risk for bleed complications.[34,35] In-vitro studies demonstrate that omega-3 fatty acids inhibit the cyclooxygenase (COX) enzyme which directly attenuate the production of thromboxane A2 from arachidonic acid.[35] This metabolic pathway diminishes the synthesis of platelet-activation factors which may attribute omega-3 fatty acids to enhanced bleeding tendencies.[35] However, studies correlating the incidence with omega-3 fatty acids in significantly eliciting bleeding complications remains inconclusive.[35] We suggest the omega-3 fatty acid content of Smoflipid may be one of many factors that could have led to this epistaxis complication, in this participant.

Limitations of this study include the heterogeneous nature, size of sample and age. As participants varied on clinical diagnosis, nutrition support regimen and age, this may be why there was no difference found on the effects of Smoflipid on liver enzymes and total bilirubin levels. To observe a true representation of the effect of Smoflipid, all participants should yield a

similar background in regards to age, clinical diagnosis, nutrition support regimen. Moreover, this study was purely an observational study and yielded a broad age group from six-months to seventeen years of age (mean age of 8.1±4.2 years). The age range in this study were older than the typical age range for when Smoflipid is typically employed. Smoflipid is normally seen implemented in neonatal intensive care units (NICU) preterm infants of younger than six-months of age. As age may play a factor in the effectiveness of Smoflipid, it may be plausible that Smoflipid may be more effective among infants of less than six-months of age. There may be a threshold of effectiveness once a certain age is reach. This could explain why Smoflipid may not achieve a significant impact on older pediatric patients with intestinal failure related PNALD. Future areas of research include examining the effects of Smoflipid beyond the NICU arena and investigating the critical period of when Smoflipid will be most effective. Another limitation includes the management and handling of missing laboratory data values. In some participants, compliance of obtaining routine lab values were not followed per protocol. A Mixed Model approach was the statistical approach to take to handle missing laboratory data values. However, obtaining all lab values can provide a better understanding on the true effects of Smoflipid. Dosing of Smoflipid is another confounding factor for this study. The maximum infusion rate of Smoflipid, per Food Drug Administration (FDA) dosage protocol, is at 0.5ml/kg/hour. Some participants were receiving Smoflipid treatments from various institutions and there was a variability in the dosing of Smoflipid infusion. Two participants had Smoflipid doses that went slightly beyond the maximum infusion rate. Furthermore, understanding the underlying mechanism of the action of the dose and overall lipid emulsion composition in it relationship of ameliorating intestinal failure related PNALD is limited.

Continuance of Smoflipid use over a longer time frame may be helpful for future research studies to see if there are further improvements. Due to the unique complications of each patient on long term TPN, a longer time frame for the study would be able to account for any hospitalizations that occured and allow for lab values to be normalized before being recorded. Furthermore, a larger and homogenous sample size is crucial to truly assess the effects of Smoflipid. Future research on assessing the effects of various Smoflipid dosage is also beneficial to understand its relationship with ameliorating PNALD. Another area of future research that shows potential is comparing the impact of pure fish oil lipid emulsion (Omegavan) versus mixed lipid emulsion (Smoflipid). According to Calkins et al.,[24] mixed lipid emulsions like Smoflipid may be perceived as "more balanced." However, research supporting the relationship between Smoflipid in preventing intestinal failure related PNALD remains conflicting. It will also beneficial to examine the optimal time period for when Smoflipid will be most effective in preventing or reducing intestinal failure related PNALD. Understanding complications of epistaxis and the effects of the omega-3 fatty acids in fish oil-base emulsions is also another venue for research. A strong and necessary area of potential research is measuring the effects of the microbiome on parenteral nutrition-dependent patients and its role in nutrient metabolism. Severe hyperglycemia was observed in one patient. After ruling out other factors that may have been contributing to the hyperglycemic response from Smoflipid, it will prove useful to understand how gut dysbiosis, in parenteral nutrition dependent patients, mitigates inflammatory pathways and affect overall nutrient metabolism and gut barrier function. Lastly, Smoflipid's impact on hemoglobin A1C and infection rates warrants future research.

Conclusion

Parenteral nutrition (PN) is critical in meeting the nutritional needs of patient who are unable to digest or absorb nutrients, enterally or orally. As Smoflipid yields a lower n-6:n-3 ratio, lower phytosterol content and higher alpha-tocopherol content, this may reduce lipid peroxidation and prevent or reduce further damage to the liver. An increasing body of evidence supports the usage of Smoflipid in preventing or reducing complications associated with PNALD. Furthermore, the higher n-3 fatty acid content may be beneficial in mitigating anti-inflammatory eicosanoid pathways.

Smoflipid shows promise in improving the quality of life by reducing TPN central line infections rates and hemoglobin A1C. Although data demonstrated statistically significant results in the reduction of central line infections and hemoglobin A1C, clinical decisions can not be made at this time on whether Smoflipid played a direct effect with these findings. Future research is needed to explore this relationship. Furthermore, it is important to note a decreasing trend in the overall mean percent change of liver enzymes (AST and ALT). Despite the fact that the reduction of liver enzymes results were not statistically significant, Smoflipid may yield potential clinical biochemical effects in reducing elevated liver enzymes associated with PNALD. In all, Smoflipid may be a beneficial alternative to the standard soybean-based lipid emulsion. It may enhance the quality of life by preventing or reducing complications associated with PNALD through improving liver function, sustaining growth, reducing inflammation and reducing TPN infection rates. Additional research is needed to further examine the effectiveness of Smoflipid on the liver to facilitate in establishing a standard protocol.

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Appendix

Informed Consent

HIPAA

LOMA LINDA UNIVERSITY

CHILDREN'S HOSPITAL

STUDY INFORMATION

Dear Patient,

I would like to introduce you to a study entitled "The Efficacy of Smoflipid on Improving Liver Function in Children with Parenteral Nutrition Associated Liver Disease. " I am collaborating with the Principal Investigator, Mrs. Kyndra Woosley, MS, RD, Assistant Professor in Nutrition and Dietetics at Loma Linda University. We will be assisted by graduate students in her department who will receive credit towards their degree.

This observational study will examine the efficacy of Smoflipid on improving liver enzymes and bilirubin levels on pediatric patients with intestinal failure who require home total parenteral nutrition (TPN). In addition, we will evaluate growth, TPN infection rates, and tolerance of Smoflipid by looking at the results of clinical tests given to children as part of their routine care.

You are invited to be in this study because you or your child:

- Have either finished 6 months of Smoflipid or are currently taking Smoflipid
- Are 6 months to 21 years of age with intestinal failure
- Are receiving home parenteral nutrition (PN) or total parenteral nutrition (TPN)
- Are followed by Pediatric TPN Clinic

Approximately 20 subjects will participate at LLU Medical Center.

If you agree to participate, you will be giving the research team permission to review your medical records in order to collection information for the study two times: before the start of Smoflipid and again at the end of six-months of Smoflipid. Your medical care will not be changed in any way.

To minimize the risk of breach of confidentiality, your name will not be recorded with our research data. Instead you will be assigned a unique study number and your identity kept separately in a secure location in the Principal Investigator's office.

Your rights regarding the use of your Protected Health Information is explained in the attached authorization form.

Loma Linda University
Adventist Health Science Center
Institutional Review Board
Approved 7/6/17 Void after 7/4/2018
#5170185 Chair

Although you are not likely to benefit personally from this study at this time, your participation may help practitioners to see if Smoflipid improves intestinal failure and provide a standard protocol for patients with intestinal failure.

Your participation in this study is entirely voluntary. You may refuse to participate or withdraw once the study has started. Your decision whether or not to participate or terminate at any time will not affect your standing with your caregivers or the researchers at Loma Linda Health. You do not give up any legal rights by participating in this study. There is no cost to you for participating in this study nor will you be paid to be included in research.

If you have any questions about the study, please call the Principal Investigator Kyndra Woosley during routine office hours at (909) 558-4593. If you have any complaints or concerns about your rights in this study, call 909-558-4647 or e-mail patientrelations@llu.edu for information and assistance.

If you wish to proceed and participate in this study after reading this information letter, please complete the attached Protected Health Information form. By completing this PHI Authorization, you are giving consent for you or your child to participate.

Thank you in advance for considering this invitation to participate

Sincerely,

Khiet DT Ngo

Khiet Ngo, D.O., M.S.
Assistant Professor
Department of Pediatrics

Loma Linda University
Adventist Health Science Center
Institutional Review Board
Approved 7/6/17 Void after, 7/4/2018
#5170185 Chair Sarah Lacy

INSTITUTIONAL REVIEW BOARD
Authorization for Use of Protected Health Information (PHI)

Per 45 CFR §164.508(b)

RESEARCH PROTECTION PROGRAMS
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TITLE OF STUDY:	The Efficacy of Smoflipid on Improving Liver Function in Children with Parenteral Nutrition Associated Liver Disease (PNALD)
PRINCIPAL INVESTIGATOR:	Mrs. Kyndra Woosley, MS, RD, Assistant Professor in Nutrition and Dietetics at Loma Linda University
Others who will use, collect, or share PHI:	Study Personnel

Use of the terms "I," "you" and "your" addresses, where appropriate, the study patient, the parent or legal representative if the study patient is a minor, any unborn fetus(es) and child(ren) once born. The study named above may be performed only by using personal information relating to your health. National and international data protection regulations give you the right to control the use of your medical information. Therefore, by signing this form, you specifically authorize your medical information to be used or shared as described below.

The following personal information, considered "Protected Health Information" (PHI) is needed to conduct this study and may include, but is not limited to: age, gender, anthropometrics (BMI, weight, height), past and current medical history, past and current surgical history, medications, medical charts, results of all the liver enzymes (AST, ALT), EFA, hemoglobin A1C, and bilirubin tests and procedures performed, and length of time on Smoflipid and current TPN regimen.

The individual(s) listed above will use or share this PHI in the course of this study with the Institutional Review Board (IRB) of Loma Linda University, and its affiliates, government agencies such as the Food and Drug Administration (FDA), other research sites involved in this study, health care providers who provide services to you in connection with this study, central labs, central review centers and central reviewers.

The main reason for sharing this information is to be able to conduct the study as described earlier in the consent form. In addition, it is shared to ensure that the study meets legal, institutional, and accreditation standards. Information may also be shared to report adverse events or situations that may help prevent placing other individuals at risk.

Loma Linda University
Adventist Health Science Center
Institutional Review Board
Approved 7/6/17 Void after 7/4/2018
#5170185 Chair

All reasonable efforts will be used to protect the confidentiality of your PHI, which may be shared with others to support this study, to carry out their responsibilities, to conduct public health reporting and to comply with the law as applicable. Those who receive the PHI may share with others if they are required by law, and they may share it with others who may not be required to follow national and international "protected health information" (PHI) regulations such as the federal privacy rule.

Subject to any legal limitations, you have the right to access any protected health information created during this study. You may request this information from the Principal Investigator named above but it will only become available after the study analyses are complete.

- This authorization does not expire, and will continue indefinitely unless you notify the researchers that you wish to revoke it.

You may change your mind about this authorization at any time. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal health information will be used for this study. However, study personnel may continue to use the health information that was provided before you withdrew your permission. If you sign this form and enter the study, but later change your mind and withdraw your permission, you will be removed from the study at that time. To withdraw your permission, please contact the Principal Investigator or study personnel at Mrs. Kyndra Woosley, MS, RD at (909) 558-1000 ext: 47242.

You may refuse to sign this authorization. Refusing to sign will not affect the present or future care you receive at this institution and will not cause any penalty or loss of benefits to which you are entitled. However, if you do not sign this authorization form, you will not be able to take part in the study for which you are being considered. You will receive a copy of this signed and dated authorization prior to your participation in this study.

.....

I agree that my personal health information may be used for the study purposes described in this form.

Signature of Patient *or* Patient's Legal Representative	**Date**
Printed Name of Legal Representative (if any)	**Representative's Authority to Act for Patient**

Loma Linda University
Adventist Health Science Center
Institutional Review Board
Approved 7/6/17 Void after 7/4/2018
#5170185 Chair

IRB 6/20/2014