JPPT | Single-Center Retrospective Study

SO,MCT,OO,FO-ILE Is Associated With Better Side Effect Profile Than SO-ILE in Critically Ill Children Receiving Parenteral Nutrition

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OBJECTIVES This study aimed to evaluate the side effect profile of soybean oil lipid injectable emulsion (SO-ILE) and soybean oil, medium-chain triglyceride, olive oil, fish oil lipid injectable emulsion (SO,MCT,OO,FO-ILE) in critically ill children requiring parenteral nutrition (PN).

METHODS This is an observational study of children admitted to our pediatric intensive care unit requiring PN for ≥7 days. Patients were divided into 2 cohorts: SO,MCT,OO,FO-ILE (n = 34) and SO-ILE (n = 111). Outcomes included development of hypertriglyceridemia (HTG), intestinal failure–associated liver disease (IFALD), length of stay, and mortality. Logistic regression was performed after controlling for duration and maximum dose of lipids.

RESULTS The median maximum lipid dose was significantly higher in the SO,MCT,OO,FO-ILE cohort (2.7 vs 3 g/kg; p = 0.01). Prevalence of baseline HTG was similar in both cohorts. After excluding patients with baseline HTG, incidence of HTG upon PN introduction was higher in the SO-ILE cohort (51.2% vs 26.7%; p = 0.02). The SO-ILE cohort also had significantly higher triglyceride concentrations at peak and upon discontinuation of PN (p < 0.05). Direct bilirubin and C-reactive protein were significantly higher in the SO-ILE cohort after stopping PN. Five patients (3.4%) developed IFALD, 4 of whom were in the SO-ILE cohort (p = 0.85). Upon logistic regression, mortality rate and incidence of HTG remained significantly higher in the SO-ILE cohort (adjusted odds ratio, 2.3 [95% CI, 1.1–5.3]; p = 0.04; and adjusted odds ratio, 2.0 [95% CI, 1.3–5.1]; p = 0.03, respectively).

CONCLUSIONS In critically ill children requiring PN, SO-ILE was associated with a higher risk of HTG, elevated direct bilirubin, inflammatory markers and mortality compared with SO,MCT,OO,FO-ILE.

ABBREVIATIONS CRP, C-reactive protein; FA, fatty acid; HTG, hypertriglyceridemia; IFALD, intestinal failure–associated liver disease; ILE, lipid injectable emulsion; IQR, interquartile range; LOS, length of stay; MO-ILE, multicomponent oil lipid injectable emulsion; PICU, pediatric intensive care unit; PN, parenteral nutrition; SO-ILE, soybean oil lipid injectable emulsion; SO,MCT,OO,FO-ILE, soybean oil, medium chain triglyceride, olive oil, fish oil lipid injectable emulsion; TG, triglyceride

KEYWORDS critical care; lipid injectable emulsion; parenteral nutrition; pediatric; triglyceride

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Introduction

Lipid injectable emulsions (ILEs) are an important macronutrient in children requiring parenteral nutrition (PN) in critical care units.[1] They are an important source of non-carbohydrate calories, essential fatty acids (FAs) and fat-soluble vitamins.[2] Until the last decade, pure soybean oil ILE (SO-ILE; Intralipid, Fresenius Kabi, Uppsala, Sweden) was used as the standard of care in most critically ill children. However, SO-ILE contains high amounts of omega-6 FA as well as phytosterols and has low amounts of α-tocopherol, which is the bioactive form of vitamin E.[3–5] This has been implicated in various adverse effects associated with SO-ILE, including development of liver disease as well as immunosuppressive effects.[6] Adult data show that SO-ILE increased the concentrations of inflammatory cytokines, like interleukin-6, in severely stressed patients.[7] Critically ill children in the pediatric intensive care unit (PICU) are often under a lot of physiologic stress. Thus, the use of SO-ILE can theoretically increase the stress response and cytokine concentrations in these patients, leading to worse outcomes.

A soybean oil, medium-chain triglyceride, olive oil, fish oil ILE (SO,MCT,OO,FO-ILE; SMOFlipid, Fresenius Kabi) was approved in the United States in 2016 as a source of calories and essential FAs in adults

receiving PN. SO,MCT,OO,FO-ILE has since become the standard of care for children requiring chronic PN in many institutions.[6] This change in practice is based on early evidence that SO,MCT,OO,FO-ILE may improve clinical outcomes, including reduced incidence of intestinal failure–associated liver disease (IFALD).[8] Adult literature also shows excellent tolerance of SO,MCT,OO,FO-ILE, with no adverse effects and potential anti-inflammatory effects.[9] A study by Tomsits et al[5] compared outcomes of premature infants on SO-ILE vs SO,MCT,OO,FO-ILE and found no statistical differences in adverse effects and weight gain between the groups, yet other growth parameters were not assessed. Another study, assessing growth and FA profiles in very low birth weight newborns on SO,MCT,OO,FO-ILE compared to those on SO-ILE, demonstrated higher weight and head circumference z-scores and a higher concentration of certain omega-3 FAs in the plasma of children on SO,MCT,OO,FO-ILE.[10] A study by Jackson et al[11] comparing SO,MCT,OO,FO-ILE to SO-ILE in 136 neonates reported significant reduction in the incidence of IFALD with the use of SO,MCT,OO,FO-ILE (16% vs 2.5%). Although initial data look promising in neonates, there is little evidence regarding the benefits of SO,MCT,OO,FO-ILE in critically ill children.

This study aimed to compare the side effect profile and growth parameters, as well as outcomes, in children receiving SO-ILE to those receiving SO,MCT,OO,FO-ILE as a part of their lipid source in the PICU.

Materials and Methods

Design and Setting. This is a retrospective chart review of children admitted to the PICU at Oklahoma Children's Hospital from January 1, 2015, to July 31, 2020, who required PN for at least 7 days supplemented with ILE. Children were divided into 2 cohorts based on the type of ILE received: SO-ILE and SO,MCT,OO,FO-ILE. The decision on initiation of PN and type of ILE provided in PN was dependent on the inpatient team's preference.

Inclusion and Exclusion Criteria. Children (age <18 years) admitted to Oklahoma Children's Hospital PICU who received PN for at least 7 days supplemented with either SO-ILE or SO,MCT,OO,FO-ILE as source of lipid were included in the study. Children with preexisting liver disease or conditions that lead to abnormal lipid profile (primary hypertriglyceridemia [HTG]) or those on home PN were excluded from the study. Patients who received PN for <7 days, children admitted to the PICU as overflow patients, and those who received PN without lipid formulation or with fish oil ILE (FO-ILE; Omegavan, Fresenius Kabi) were also excluded from the study.

Data Collection. All data were collected by a review of electronic medical records. Demographic data included age, sex, ethnicity, and admission and discharge weight (in kilograms). Clinical data included primary diagnosis (system involved), duration, and maximum dose of lipids received. Laboratory markers included liver profile, including aspartate transaminase, alanine transaminase, total and direct bilirubin, serum triglyceride (TG) concentration, serum creatinine, and C-reactive protein (CRP) at baseline, their peak concentrations and a measurement after discontinuation of PN. Outcomes of interest included development of HTG defined as serum TG ≥150mg/dL (based on laboratory cutoff value at our institution) with a normal baseline TG value, IFALD defined as direct bilirubin ≥2 mg/dL with a normal baseline direct bilirubin, hospital length of stay (LOS), and in-hospital mortality.

Statistical Analysis. Continuous data were expressed as median and interquartile range (IQR) and compared between the 2 cohorts using the Wilcoxon rank sum test. Categoric data were represented as number and percentages and compared using the χ^2 or Fisher exact tests as appropriate. Logistic regression was performed after adjusting for the duration and maximum dose of lipids to evaluate outcomes. Statistical analysis was performed using JMP Pro, version 14.0 (SAS Institute, Cary, NC). A p value <0.05 was considered statistically significant.

Results

A total of 145 patients were included in the study, 111 (76.6%) in the SO-ILE cohort and 34 (23.4%) in the SO,MCT,OO,FO-ILE cohort. Table 1 provides a comparison of demographics of patients among the 2 cohorts. There was no difference in age at admission, sex, ethnicity, admission weight, and primary diagnosis system between the 2 groups. There was a predominance of males in both groups (59.5% in SO-ILE vs 64.7% in SO,MCT,OO,FO-ILE group; p = 0.58). Most of the patients in both groups were white (64.9% in SO-ILE vs 61.8% in the SO,MCT,OO,FO-ILE group). The most common system of primary diagnosis in both groups was cardiac followed by respiratory (p = 0.22). Compared with SO,MCT,OO,FO-ILE, the SO-ILE cohort had a longer median duration of ILE use (14 days vs 11 days; p = 0.04) and lower maximum lipid dose (2.7 vs 3 g/kg; p = 0.01).

Table 2 compares the laboratory values and outcomes of patients among the 2 cohorts. On comparing baseline labs, median serum TG was significantly higher in the SO-ILE group (104 vs 71 mg/dL; p = 0.002). Baseline HTG was observed in 29 patients, with no statistical difference among the 2 cohorts (22.5% in the SO-ILE group vs 11.8% in the SO,MCT,OO,FO-ILE group; p = 0.15). There was no difference in baseline liver function and inflammatory markers between the groups. Peak median TG concentrations were also significantly higher in the SO-ILE group (164 mg/dL vs 109.5 mg/dL; p = 0.0005), whereas there was no difference in other lab data. At the discontinuation of PN, serum TG, direct bilirubin, and CRP concentrations were higher in the SO-ILE group. After excluding the

Table 1. Baseline Demographics of Critically Ill Children Requiring Lipid Injectable Emulsion For ≥7 Days

Characteristic	SO-ILE (n = 111)	SO,MCT,OO,FO-ILE (n = 34)	p value
Age on hospital admission, median (IQR), mo	1.02 (0.00–12.92)	0.25 (0.00–6.67)	0.53
Admission weight, median (IQR), kg	4.90 (3.00–9.45)	3.33 (2.81–6.45)	0.09
Sex, n (%)			
Male	66 (59.46)	22 (64.71)	0.58
Ethnicity, n (%)			0.86
White	72 (64.86)	21 (61.76)	
African American	10 (9.01)	4 (11.76)	
Asian	1 (0.9)	0	
Hispanic	5 (4.5)	3 (8.82)	
Native American	9 (8.11)	3 (8.82)	
Other	14 (12.61)	3 (8.82)	
Primary diagnosis system, n (%)			0.22
Cardiac	70 (63.1)	25 (73.5)	
Gastrointestinal	8 (7.2)	2 (5.9)	
Respiratory	15 (13.5)	5 (14.7)	
Hematologic	6 (5.4)	0 (0)	
Immune system	9 (8.1)	1 (2.9)	
Miscellaneous	3 (2.7)	1 (2.9)	
Lipid injectable emulsion, median (IQR)			
Duration of lipids, days	14 (9–24)	11 (9–14)	0.04
Maximum dose, g/kg	2.7 (2–3.1)	3 (2.5–4)	0.01

SO-ILE, soybean oil lipid injectable emulsion; SO,MCT,OO,FO-ILE, soybean oil, medium-chain triglyceride, olive oil, fish oil lipid injectable emulsion

patients with baseline HTG, the number of patients who developed HTG after starting PN was significantly higher in the SO-ILE group (51.2% vs 26.7%; p = 0.02). A total of 5 patients (3.4%) developed IFALD, of whom 4 were in the SO-ILE cohort (p = 0.85). Median discharge weight and hospital LOS were similar in both groups. The mortality rate was 58.6% in the whole cohort, with a higher mortality rate observed in the SO-ILE group (64.9% vs 38.2%; p = 0.006).

Logistic regression was performed after adjusting for the duration and maximum dose of lipids and outcomes were compared between the SO-ILE and SO,MCT,OO,FO-ILE groups. Adjusted odds ratio for mortality after logistic regression was 2.3 (95% CI, 1.1–5.3; p = 0.04), suggesting SO-ILE had a higher mortality compared with SO,MCT,OO,FO-ILE. Although SO-ILE was associated with an increased length of stay after adjusting for duration and maximum dose of lipids, this was not statistically significant (p = 0.07). Adjusted odds ratio for HTG in the SO-ILE group after adjusting for duration and maximum dose of ILE, as well as baseline HTG, was 2.0 (95% CI, 1.3–5.1; p = 0.03). Given the low incidence of IFALD, we could not perform logistic regression for this outcome.

Discussion

Our study compares biochemical profiles and outcomes of critically ill children on SO-ILE vs SO,MCT,OO,FO-ILE. The results of this study show that the use of SO-ILE is associated with the development of HTG, direct bilirubin, as well as an increase in inflammatory markers. Along with a lower incidence of HTG after initiation of PN, SO,MCT,OO,FO-ILE was also associated with lower TG concentrations throughout admission and upon discontinuation of PN. SO,MCT,OO,FO-ILE was also associated with significantly lower mortality compared with SO-ILE. Most studies comparing the safety of SO-ILE vs SO,MCT,OO,FO-ILE have been performed in the neonatal population or adults. There is a paucity of data in critically ill children admitted to the PICU receiving ILE as a part of PN. To our knowledge, this is a novel finding in this particular patient population.

Varying results have been seen in both adult and neonatal populations with respect to the effect of ILE on the serum TG concentration. A randomized clinical trial in 35 adults undergoing gastrointestinal surgery showed a lower rise in serum TG concentrations in patients receiving SO,MCT,OO,FO-ILE compared with MCTs/long-chain triglycerides (Lipovenoes, Fresenius Kabi).[12] Similarly, 2 other adult studies showed lower serum TG concentrations with multicomponent oil ILE (MO-ILE), mainly attributed to faster clearance of SO,MCT,OO,FO-ILE.[13,14] However, various other studies performed in adults showed no difference in serum TG values between patients on SO-ILE vs MO-ILE.[5,15,16] Another study performed

Table 2. Comparison of Laboratory Values and Outcomes of Patients on Soybean Oil Lipid Injectable Emulsion (SO-ILE) vs Soybean Oil, Medium-Chain Triglyceride, Olive Oil, Fish Oil Lipid Injectable Emulsion (SO,MCT,OO,FO-ILE)

Characteristics	SO-ILE (n = 111)	SO,MCT,OO,FO-ILE (n = 34)	p value
Baseline, median (IQR)			
AST, units/L	50 (28–103)	41 (30–75)	0.40
ALT, units/L	23 (13–44)	30.5 (14–49)	0.35
Triglycerides, mg/dL	104 (72–148.5)	71 (43–119)	0.002
Bilirubin, total, mg/dL	0.7 (0.3–3.6)	0.65 (0.4–1.5)	0.93
Bilirubin, direct, mg/dL	0.5 (0.2–0.95)	0.4 (0.15–0.7)	0.40
Creatinine, mg/dL	0.41 (0.25–0.62)	0.36 (0.21–0.61)	0.51
CRP, mg/L	17.5 (2–54.6)	17.3 (4.3–43.8)	0.96
Peak labs, median (IQR)			
AST, units/L	106 (64–285)	96 (40–169)	0.20
ALT, units/L	59 (26–155)	52 (28–109)	0.73
Triglycerides, mg/dL	164 (113–262.5)	109.5 (52–189)	0.0005
Bilirubin, total, mg/dL	1.6 (0.4–5.9)	1 (0.6–2)	0.20
Bilirubin, direct, mg/dL	0.8 (0.2–3.4)	0.4 (0.2–0.75)	0.06
Creatinine, mg/dL	0.58 (0.35–0.92)	0.47 (0.34–0.86)	0.39
CRP, mg/L	44.75 (17–135.2)	50.1 (23.35–75.75)	0.52
Labs at discontinuation of PN, median (IQR)			
AST, units/L	49 (32–85)	43 (30–70.5)	0.23
ALT, units/L	31.5 (17–69)	29 (17–61)	0.58
Triglycerides, mg/dL	134 (88–194)	84.5 (45–136)	0.002
Bilirubin, total, mg/dL	0.45 (0.2–1.4)	0.5 (0.35–0.85)	0.94
Bilirubin, direct, mg/dL	0.6 (0.1–3.4)	0.2 (0.1–0.4)	0.017
Creatinine, mg/dL	0.4 (0.27–0.82)	0.29 (0.22–0.62)	0.12
CRP, mg/L	27.2 (12.7–87.4)	16.6 (7.5–31.25)	0.017
Baseline hypertriglyceridemia, n (%)	25 (22.5)	4 (11.8)	0.15
Hypertriglyceridemia with PN, n (%)	44 (51.2)	8 (26.7)	0.02
Discharge weight, median (IQR), kg	7 (3.7–10.6)	6.2 (4–8.9)	0.39
Hospital length of stay, median (IQR), days	65 (38–176)	56 (30–105)	0.28
Mortality, n (%)	72 (64.9)	13 (38.2)	0.006

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; IQR, interquartile range; PN, parenteral nutrition

in extremely premature infants receiving PN showed no difference in the incidence of HTG and severe HTG in patients on SO-ILE vs SO,MCT,OO,FO-ILE.[17] Pichler et al[18] showed similar results in children with intestinal failure receiving PN.

Our study showed significantly lower direct bilirubin concentrations at the discontinuation of PN in patients who received SO,MCT,OO,FO-ILE compared with those on SO-ILE; however, the total bilirubin concentrations were similar in both groups. Varying results have been seen in studies with respect to liver function among different patient populations. Significant reduction in bilirubin concentrations with SO,MCT,OO,FO-ILE compared with SO-ILE has been reported, especially in children with intestinal failure. A retrospective study performed by Daniel et al[19] in pediatric patients on PN showed significantly lower incidence of IFALD in patients on MO-ILE compared with SO-ILE (p = 0.03). Other studies performed in infants with intestinal failure or those on PN for more than 2 weeks showed similar results.[11,20] A double-blind randomized study by Goulet et al[21] in pediatric patients on home PN showed a higher change in serum bilirubin in patients after starting on SO,MCT,OO,FO-ILE compared with those on SO-ILE, with a significant decrease in the bilirubin concentration seen in those on SO,MCT,OO,FO-ILE. Pichler et al[18] showed a significant reduction in alanine transaminase after using SO,MCT,OO,FO-ILE in children with intestinal failure; however, no differences in total and direct bilirubin were noted. Another study performed in infants with intestinal failure showed a similar incidence of cholestasis in both groups, but quicker resolution of hyperbilirubinemia was seen in the SO,MCT,OO,FO-ILE group compared with the SO-ILE group.[22] A difference in the incidence of IFALD was not found between the

cohorts in our study; however, this could be due to an overall low incidence of IFALD in both cohorts.

SO,MCT,OO,FO-ILE was also associated with a lower inflammatory profile with a lower CRP at discontinuation of PN in our study. Various studies in adults have shown that addition of fish oil to soybean oil as ILE in patients with sepsis has been associated with lowering of CRP values.[23,24] The study by Pichler et al[18] in children with intestinal failure showed a significant reduction in CRP after switching from SO-ILE to SO,MCT,OO,FO-ILE ($p = 0.02$). A study by Wischmeyer et al[25] showed a decrease in the incidence of pneumonia and hospital LOS for children admitted to the PICU after switching to SO,MCT,OO,FO-ILE. We did not find a statistically significant difference in hospital LOS between the 2 groups.

Mortality was significantly higher in SO-ILE group in this study ($p = 0.006$). Another study in critically ill children in PICU showed no difference in mortality between patients receiving different ILEs.[26] Although some confounders could not be completely accounted for and may potentially explain this discrepancy, we adjusted for the duration and maximum dose of lipids among the 2 groups using logistic regression, and adjusted odds ratio for mortality was still high in the SO-ILE group.

Some of the above results can be attributed to the overall composition of SO,MCT,OO,FO-ILE compared with SO-ILE. SO,MCT,OO,FO-ILE, a mixed ILE comprising different lipid sources: soybean oil (30%), which provides essential FA; olive oil (25%), high in monounsaturated FA less susceptible to peroxidation; and MCT (30%) and fish oil (15%), which are rich in the anti-inflammatory omega-3 FA.[4,6] Exclusively SO-ILE is rich in omega-6 FA and phytosterols, which are pro-inflammatory in nature.[6] Conversely, omega-3 FA decreases hepatic levels of the enzyme-soluble epoxide hydrolase, which in turn decreases the degradation of anti-inflammatory molecules.[8]

This study has some limitations. Because of its retrospective nature and small sample size, there is a possibility of potential unknown confounders being missed. Moreover, this is a single-center study; thus, the findings may not be generalizable. Finally, because the decision on the type of ILE to be given depended on the inpatient team, there could be a bias related to provider preference for a certain type of ILE. It is possible that some patients with an abnormal liver biochemical profile were started on SO,MCT,OO,FO-ILE; however, no difference in liver enzymes at baseline existed among the 2 groups. Because of limited data availability, we were not able to compare the groups based on critical illness scores.

Conclusion

Formulations with a lower inflammatory profile, like SO,MCT,OO,FO-ILE, may be helpful in preventing some complications, particularly HTG, which seems to have an earlier onset once PN has been initiated. SO,MCT,OO,FO-ILE was also associated with significantly lower mortality compared with the SO-ILE cohort. Further studies evaluating the progression to IFALD by incorporating other parameters, such as degree of thrombocytopenia, coagulopathy, and albumin levels, would be beneficial.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution (University of Oklahoma Institutional Review Board; IRB No. 12601, October 13, 2020). Given the nature of this study, informed consent was not required.

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