Use of a Mixed-Oil Lipid Emulsion in Infants with Intestinal Failure Associated Liver Disease who were Receiving a Soybean Oil Emulsion

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Abstract

Introduction: Parenteral nutrition (PN) is crucial to sustain life and ensure adequate growth in infants with gastrointestinal disease. Soybean-oil injectable lipid emulsion (SO-ILE) as a component of prolonged PN has been associated with intestinal failure-associated liver disease (IFALD). A mixed-oil ILE (MO-ILE) may avoid this problem by providing a more balanced fatty acid profile. The purpose of our study was to examine serum bilirubin to determine if the use of a MO-ILE reverses IFALD in PN-dependent infants who had received SO-ILE.

Methods: This was a single-center retrospective study of infants < 1 year of age who received PN for ≥ 4 weeks and received MO-ILE. The primary outcome was resolution of elevated bilirubin concentration in infants who changed from SO-ILE to MO-ILE.

Results: A total of 16 infants receiving SO-ILE who developed an elevated bilirubin and were switched to MO-ILE were included in the analysis. PN and SO-ILE were initiated at a median of 1 (0 - 64) day of life. IFALD onset was 22 ± 15 d after the initiation of PN. MO-ILE was started a median of 8 days (0 - 145 days) from the onset of IFALD. Fifteen infants had resolution of the IFALD after an average of 57 ± 36 days of MO-ILE. Three of the 15 infants had resolution prior to the initiation of enteral feeds, the remaining 12 infants had resolution after 58 ± 36 days of consistent enteral feedings. The infant who did not have resolution of IFALD died two weeks after starting MO-ILE.

Conclusion: MO-ILE was associated with resolution of elevated bilirubin concentrations although the impact cannot be separated out from the effect of enteral feeding. While this study supports the use of MO-ILE, future studies are needed to determine if MO-ILE initiated at the onset of PN will prevent or lower the incidence of developing of IFALD.

Keywords: Lipid Emulsions; Liver Disease; Infants; Parenteral Nutrition

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Abbreviations


Introduction

Parenteral nutrition (PN) is a lifesaving intervention that has been used for many years in infants with gastrointestinal disease [1,2]. To ensure adequate growth and development, long-term PN is often required. However, the long-term use of PN is associated with a number of severe adverse effects including sepsis, metabolic abnormalities and liver disease. Intestinal failure-associated liver disease (IFALD) is a frequent and life-threatening complication seen in up to two-thirds of infants on long-term PN with mortality reaching up to 50% [3,4]. Known patient risk factors for IFALD include low birth weight, prematurity, immature liver function, short bowel syndrome, lack of enteral feeding, and sepsis [5,6]. PN factors include duration of administration, amino acid composition and dose, excess carbohydrate administration, lipid injectable emulsion (ILE) composition and dose, aluminum toxicity, plasticizing agent in tubing and drug therapy [7,8]. The conventional ILE is a soybean-oil ILE (SO-ILE) that contains a higher predominance of pro-inflammatory omega-6 fatty acids [9]. Further, SO-ILE may lead to depletion of antioxidant defenses due to the limited amount of alpha-tocopherol and the presence of phytosterols that may lead to dysregulation of bile acid synthesis and transport [10,11]. These characteristics of SO-ILE have the potential to exert negative effects on hepatic function leading to development of IFALD that has led to management and prevention strategies that include the use of alternative fish oil-based ILE and lipid restriction [12]. There are increasing available alternative oil options for ILE besides soybean oil, including olive oil, medium chain triglycerides (MCT), and fish oil. In 2016 the FDA approved a mixed-oil ILE (MO-ILE) containing soybean oil, MCT, olive oil, and fish oil for use in adults. Previous studies have shown improvements with MO-ILE compared to SO-ILE in neonates with IFALD [13,14]. However, additional evidence is needed to strengthen MO-ILE’s position in clinical practice.

Purpose of the Study

The purpose of our study was to examine serum bilirubin to determine if the use of a MO-ILE reverses IFALD in PN-dependent infants who had received SO-ILE.

Materials and Methods

This was a single center retrospective observational study that was approved by our University of Tennessee’s Institutional Review Board. In November 2016 the Pharmacy and Therapeutics Committee approved the use of MO-ILE (SMOFlipid) in infants who developed a direct bilirubin ≥ 2 mg/dL or total bilirubin ≥ 4 mg/dL while receiving PN with SO-ILE (Intralipid). All infants who received at least 4 weeks of PN between December 1, 2016 and December 31, 2017 had their electronic medical records reviewed to identify infants who received MO-ILE. The data extracted from the electronic medical record included: patient characteristics (gender, gestational age, race, birth weight, diagnoses, bowel resection), age PN initiated, PN duration when direct bilirubin ≥ 2 mg/dL was detected, PN duration at peak bilirubin, duration of elevated bilirubin before MO-ILE was initiated and IFALD outcomes (resolution of elevated bilirubin, duration of MO-ILE until resolution of elevated bilirubin, and total duration of PN). The timing of consistent enteral feedings was defined as no suspensions or interruptions except for limited time for procedures such as extubation. Data was censored at discontinuation of PN, discharge/transfer to another facility, the end of our study period (12/31/17) or death, whichever came sooner. Patients were excluded if they started MO-ILE prior to the development of a direct bilirubin ≥ 2 mg/dL, developed elevated direct bilirubin while on extracorporeal membrane oxygenation (ECMO), or had an elevated direct bilirubin before the start of PN. Data analysis was a descriptive summation of the results and included percent, mean and standard deviation (SD) and median and range.

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Results

A total of 353 infants received PN during the study period. Of these, 54 (15.3%) infants received PN for more than 4 weeks. Figure 1 illustrates the fate of these 54 infants. Of the 54 patients, 34 infants received at least one day of MO-ILE. Elevated bilirubin did not occur in 26 of the total 54 infants (48%), although 10 of these infants received MO-ILE. Four infants received MO-ILE prior to their elevated bilirubin meeting the criteria, 2 infants who received MO-ILE developed elevated bilirubin during ECMO therapy and 2 infants had elevated bilirubin prior to starting PN. This resulted in 16 infants being included in the final analysis. There were four infants who had an elevated bilirubin but did not receive MO-ILE. The patient characteristics are summarized in table 1. Patients were predominantly male (13) and African American (9). Mean gestational age and birth weight were 30 ± 5 weeks and 1217 ± 714 grams. The majority of these PN-dependent infants had a diagnosis of necrotizing enterocolitis and had a portion of their bowel resected. PN was initiated at a median of 1 (0 - 64) day of life. These infants received daily PN that included amino acids at 2.5 to 3.5 g/kg/day and SO-ILE at 2 to 3 g/kg/day. The dose of protein and ILE did not change when switched to MO-ILE. Direct Bilirubin concentrations was ≥ 2 mg/dL after 22 ± 9 days of PN with SO-ILE. Direct bilirubin were elevated for a median of 8 (0 - 145) days before the initiation of MO-ILE. The peak direct bilirubin concentration occurred at 53 ± 9 days of PN. In 14 of 16 infants the peak bilirubin occurred a median of 14 (0 - 55) days after starting MO-ILE. Two patients had their peak bilirubin prior to starting MO-ILE. Consistent enteral feedings were initiated at 66 ± 54 days of age. Figure 2 illustrates the weekly direct bilirubin concentrations after the start of MO-ILE. Table 2 shows the outcomes of the 16 infants with IFALD who received MO-ILE. Fifteen of the 16 infants had resolution of their elevated bilirubin 57 ± 36 days after MO-ILE was started. The one patient who did not have resolution died two weeks after the initiation of MO-ILE. Three of the 15 patients had resolution of their elevated bilirubin prior to consistent enteral feeds, the remaining 12 infants had resolution after 58 ± 36 days of consistent enteral feeds. Two of the infants had resolution of their elevated bilirubin 7 and 69 days after discontinuing PN, the remaining 13 patients continued to receive PN for a median of 87 (5 - 694) days after resolution of elevated bilirubin.

Figure 1: Disposition of infants who receive > 4 weeks of PN.

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender - no.</td>
<td>Male/Female 13/3</td>
</tr>
<tr>
<td>Race - no. (%)</td>
<td>African American 9 (56)</td>
</tr>
<tr>
<td></td>
<td>Caucasian 4 (25)</td>
</tr>
<tr>
<td></td>
<td>Other 3 (19)</td>
</tr>
<tr>
<td>Mean Gestational Age, weeks (± SD)</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>Mean Birth Weight, grams (± SD)</td>
<td>1217 ± 714</td>
</tr>
<tr>
<td>Median Age PN Initiated, days (range)</td>
<td>1 (0-64)</td>
</tr>
<tr>
<td>Diagnosis (n), (Bowel Resection (n))</td>
<td>Necrotizing enterocolitis 11 (9)</td>
</tr>
<tr>
<td></td>
<td>Gastrochisis 1 (1)</td>
</tr>
<tr>
<td></td>
<td>Inguinal hernia 1 (1)</td>
</tr>
<tr>
<td></td>
<td>Omphalocele 1 (0)</td>
</tr>
<tr>
<td></td>
<td>Tracheoesophageal fistula 1 (0)</td>
</tr>
<tr>
<td></td>
<td>Hypoplastic left heart 1 (0)</td>
</tr>
<tr>
<td>Mean Duration PN + SO-ILE Direct Bilirubin ≥ 2 mg/dL, days, (± SD)</td>
<td>22 ± 15</td>
</tr>
<tr>
<td>Mean Duration PN Peak Direct Bilirubin, days (± SD)</td>
<td>53 ± 30</td>
</tr>
<tr>
<td>Median Duration Elevated Bilirubin Before Start of MO-ILE, days (range)</td>
<td>8 (0-145)</td>
</tr>
<tr>
<td>Mean Duration PN Consistently Enterally Fed, d (± SD)</td>
<td>66 ± 54</td>
</tr>
</tbody>
</table>

Table 1: Patient characteristics (n = 16).

Figure 2: Individual weekly serum direct bilirubin concentrations after starting MO-ILE in infants who develop elevated direct bilirubin concentration while receiving PN and SO-ILE.

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The 4 infants who had elevated bilirubin but did not receive MO-ILE also had resolution of their elevated bilirubin concentration. These 4 infants had a later onset of elevated bilirubin concentration 44 days vs 22 days and had a lower peak total bilirubin 6.1 mg/dL vs 12.6 mg/dL than the MO-ILE treated infants.

Discussion

Progression of IFALD is one of the most significant causes of morbidity and mortality in infants who require long-term PN. The underlying causes of IFALD are complex and interrelated and include patient related factors like prematurity and sepsis as well as PN related factors, with much of the recent research focus on the ILE component [10,12,15]. ILE provide essential fatty acids, and is an energy-rich source of calories, and is key for the construction of important components in almost all tissues [16]. In addition, ILEs provide essential fatty acids that serve as precursors for important signaling molecules that affect a multitude of cellular processes. The conventional ILE is a SO-ILE containing high amounts of the essential long-chain polyunsaturated fatty acids (LC-PUFA) in the form of both omega-6 and omega-3 fatty acids, with a much higher predominance of omega-6 fatty acids. The omega-6 fatty acids such as arachidonic acid (ARA) lead to production of pro-inflammatory eicosanoids while the omega-3 fatty acids result in synthesis of anti-inflammatory eicosanoids [9]. SO-ILE may also lead to depletion of antioxidant defenses due to a higher content of LC-PUFAs, which are susceptible to lipid peroxidation and a limited amount of alpha-tocopherol, the primary lipophilic antioxidant [10]. The presence of phytosterols in soybean oil may lead to dysregulation of bile acid synthesis and transport [11]. The currently available MO-ILE is a mixture of soybean oil, medium chain triglycerides (MCT), olive oil, and fish oil at ratios of 30%, 30%, 25% and 15%, respectively. The fish oil component of MO-ILE helps generate a lower ratio omega-6: omega-3 fatty acids than that seen with SO-ILE, resulting in favorable inflammatory and immuno-modulatory effects. Olive oil has abundant oleic acid which, along with MCT are less susceptible to lipid peroxidation than LC-PUFA [17]. In addition, MO-ILE lipid contains adequate amounts of alpha-tocopherol and less phytosterols [10]. MO-ILE provides a more balanced supply of lipids compared to the most commonly used SO-ILE. Higher amounts of omega-3 fatty acids may prevent or reduce liver damage through increased production of anti-inflammatory eicosanoids, improved bile flow, and increased clearance and hepatic uptake of lipids [12]. Recent attention has been given to the phytosterol component in SO-ILE, which has been shown to inhibit bile acid secretion and transport in animal studies. Although current understanding of this concept is limited, recent studies have shown that farnesoid X receptor antagonism by phytosterols may be a primary mechanism [18-20]. Additionally, blood concentrations of phytosterols have been closely associated with IFALD in both children and adults [11].

In the current study, the percent of infants who received PN for at least 4 weeks (15.3%) was similar to our historical experience (16.8%) and the percent of infants (48%) who did develop an elevated direct bilirubin level (> 2 mg/dL) for any reason was similar to published data and our prior experience [3,4,21]. Resolution of IFALD was observed in 15 of 16 (94%) infants who were switched to MO-ILE. Historically, we have observed about 60% of IFALD infants who continued to receive SO-ILE had resolution of IFALD prior to discharge from the hospital [21]. Our results compare favorably to those of Muhammed., et al. who observed 62.5% of infants switch to MO-ILE had resolution of IFALD compared to only 22% who continued with SO-ILE [22]. A randomized trial examining MO-ILE vs SO-ILE at preventing

### Table 2: Intestinal failure-associated liver disease outcomes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
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<tbody>
<tr>
<td>Resolution of Elevated Bilirubin</td>
<td>15*/16</td>
</tr>
<tr>
<td>Mean Duration MO-ILE until Resolution of Elevated Bilirubin, days (± SD)</td>
<td>57 ± 36</td>
</tr>
<tr>
<td>Mean Total Duration PN, days (range)</td>
<td>254 ± 264</td>
</tr>
</tbody>
</table>

*1 patient died 2 weeks after initiating MO-ILE.
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the progression of IFALD found that 73% of MO-ILE treated infants had resolution of IFALD compared to 31% of SO-ILE treated patients [23]. While there is much clinical evidence supporting the reduction of PN duration, early initiation of enteral feeding and achieving enteral autonomy, the reduction of the ILE dose or using fish-oil ILE as prevention and treatment strategies for IFALD; there is significantly less evidence that exists for the use of MO-ILE [14,23-28].

While this study presents promising results for MO-ILE, there are some limitations that must be considered. First and foremost are the small sample size and retrospective nature of this study. It was also conducted in a single referral center which may limit the external validity for other institutions with different populations. Also, since this hospital did not have a birthing center, infants were transferred from outside hospitals which impairs our ability to account for ILEs given prior to admission. Lastly, it is important to note that enteral feeds were not initiated in a consistent manner until around the same time that direct bilirubin levels began to fall. Although it is unknown to what degree consistent enteral feeds contributed to the resolution seen in the infants, it is important to take this into account when examining MO-ILE’s efficacy in treating IFALD.

Conclusion

This year-long analysis of infants receiving prolonged PN showed resolution of IFALD in individuals transitioned from SO-ILE to MO-ILE. Our findings are consistent with previous studies in showing the hepatoprotective effect of MO-ILE and serve as additional evidence for its utility in clinical practice. We conclude that MO-ILE may preserve liver function in infants with IFALD and represents a significant advancement in ILE formulations. Future studies are needed to determine if starting MO-ILE at the onset of PN will aid in preventing the development of IFALD.

Financial Support

None.

Conflicts of Interest

Michael Christensen is on the Data Safety and Monitoring Board for SMOFlipid clinical trials sponsored by Fresenius Kabi.

Bibliography


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