Incidence and Development of Cholestasis in Surgical Neonates Receiving an Intravenous Mixed-Oil Lipid Emulsion

Lumeng J. Yu, MD\textsuperscript{1,2†}; Lorenzo Anez-Bustillos, MD, MPH\textsuperscript{1,2†}; Paul D. Mitchell\textsuperscript{3}; Victoria H. Ko, MD\textsuperscript{1,2}; Jordan D. Secor, MD, MSc\textsuperscript{1,2}; Alexis Potemkin Hurley, RN, BSN\textsuperscript{1,2}; MSc; Duy T. Dao, MD, MPH\textsuperscript{1,2}; Scott C. Fligor, MD\textsuperscript{1,2}; Bennet S. Cho, MD\textsuperscript{1,2}; Savas T. Tsikis, MD\textsuperscript{1,2}; Kathleen M. Gura, PharmD, RPh\textsuperscript{4}; and Mark Puder, MD, PhD\textsuperscript{1,2*}

\textsuperscript{1} Vascular Biology Program, Boston Children’s Hospital, Harvard Medical School, Boston, MA 02115, USA
\textsuperscript{2} Department of Surgery, Boston Children’s Hospital, Harvard Medical School, 300 Longwood Ave, Fegan 3, Boston, MA 02115, USA
\textsuperscript{3} Institutional Centers for Clinical and Translational Research, Boston Children’s Hospital, Boston, MA 02115, USA
\textsuperscript{4} Department of Pharmacy, Boston Children’s Hospital, Boston, MA 02115, USA
*Correspondence to: mark.puder@childrens.harvard.edu

† These authors contributed equally to this work.

\textbf{Background:}
Soybean oil lipid emulsions (SOLE) are the only approved initial parenteral lipid source for children, but may lead to intestinal failure-associated liver disease (IFALD). A mixed-oil lipid emulsion (MOLE) containing soybean oil is used off-label in PN-dependent children, but may not prevent IFALD.

\textbf{Methods:}
Data was retrospectively collected from neonates with gastrointestinal surgical conditions necessitating PN for ≥14 days and receiving MOLE (SMOFlipid), from July 2016 until July 2019. Unpaired and pair-matched historical surgical neonates treated with pure SOLE (Intralipid) served as controls. The primary outcome measure was development of cholestasis (direct bilirubin ≥ 2 mg/dL).

\textbf{Results:}
Overall, 152 patients were included in the final analysis. 63% (10/16) of MOLE patients developed cholestasis, while 22% (30/136) of SOLE patients developed cholestasis after at least 14 days of therapy (p=0.005). Pair-matched analysis also revealed higher rate of cholestasis in MOLE patients. The latency to developing cholestasis was significantly shorter in MOLE patients than SOLE patients. There were no significant differences in anthropomorphic data (weight-, length-, or head circumference-for age Z scores), and no subjects developed essential fatty acid deficiency in either the MOLE or SOLE groups. However, MOLE administration correlated with higher transaminase and triglyceride levels.

\textbf{Conclusion:}
MOLE does not prevent the development of cholestasis in high-risk surgical neonates and cannot be considered a hepatoprotective lipid emulsion in this patient population. Post-surgical neonates should be closely monitored for the development of IFALD, regardless of the use of MOLE versus SOLE.
Table 1. Incidence of cholestasis during study period.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>N</th>
<th>SOLE</th>
<th>MOLE</th>
<th>OR (95% CI)</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>152</td>
<td>30/136</td>
<td>10/16</td>
<td>5.89 (1.98 – 17.52)</td>
<td>140</td>
<td>6.16 (1.76 – 21.57)</td>
<td>0.005</td>
</tr>
<tr>
<td>Matched 1:1</td>
<td>18</td>
<td>2/9 (22%)</td>
<td>7/9 (78%)</td>
<td>12.3 (1.3 – 113.0)</td>
<td>18</td>
<td>9.00 (1.07 – 76.01)</td>
<td>0.044</td>
</tr>
<tr>
<td>Matched 2:1</td>
<td>27</td>
<td>3/18 (17%)</td>
<td>7/9 (78%)</td>
<td>17.5 (2.4 – 129.5)</td>
<td>27</td>
<td>13.3 (1.9 – 90.9)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*The total population was adjusted for baseline DB and number of available DB measurements, determined by stepwise logistic regression. Additional candidate predictors included baseline post-menstrual age, baseline weight-for-age Z-score, total days followed, total phytosterols, percent of calories due to PN, and diagnosis (NEC; atresia; omphalocele; gastroschisis; intestinal perforation). The matched analyses are unadjusted (no subjects were cholestatic at baseline). MOLE, Mixed-oil Lipid Emulsion; SOLE, Soybean Oil Lipid Emulsion.