Parenteral nutrition-associated cholestasis; a comparison between soy-based lipids and mix-based lipids in the high-risk surgical neonates

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Abstract

Introduction:

Parenteral nutrition-associated cholestasis (PNAC) in surgical neonates remains the most challenging complication associated with administering parenteral nutrition (PN). This is because surgical neonates are already under significant immune and metabolic stress compared to older children. This study compares the risk of PNAC developed in surgical neonates receiving Soy-based Lipids (IL) to those receiving Mix-based lipids (SL).

Method:

Sophisticated criteria are set to ensure equality of conditions and eliminate the factors that may invariably affect the results. The incidence and severity of PNAC are compared after 3 weeks of significant administration of lipid emulsion taking into consideration the control over the concomitant factors.

Results:

67 patients were included, 35 patients were in the IL group whilst 32 patients were in the SL group. There was no statistical significance between the 2 groups concerning the concomitant factors. After 21 days of being on >= 2g/kg/day of lipid emulsion, the cumulated incidence of PNAC in the IL group was 57% compared to 22% in the SL group. The absolute risk reduction (ARR) of SL is 35.27% whereas the odd ratio (OR) of IL is 4.76. The elevation of conjugated bilirubin and gamma-glutamyl transferase was about 50% less in the SL group but without statistical significance for the latter. Considering the premature surgical neonates, the ARR of SL and the OR of IL failed to prove statistical significance.

Conclusion:

The incidence and severity of PNAC are less in surgical neonates on SL compared to their counterparts on IL. However, these benefits are unclear in premature surgical neonates. The risk of PNAC in surgical neonates remains the highest, thus consideration of an alternative approach is recommended.

Introduction

The use of Parenteral Nutrition (PN) was a milestone in the history of neonatal care; it led to increased survival of infants who were malnourished as a result of their medical, traumatic or surgical illnesses that restricted the use of gastrointestinal tract [1].

The PN is comprised of three major components: carbohydrates, proteins and lipids, in addition to essential electrolytes, vitamins and trace elements. The carbohydrates and lipids serve as a source of energy for the body's daily functions, while the protein component is required as a building block for
growth and healing. Lipids have the highest calorie index (about 10 kilocalories per gram) to provide the body with essential fatty acids.

Parenteral nutrition-associated cholestasis (PNAC) is associated with high morbidity and is considered one of the most challenging conditions associated with the administration of PN [2] [3]. Although the development of PNAC is multifactorial, lipid administration is a major precursor to PNAC [4]. The use of intravenous soybean-based lipids, such as Intralipid (IL), is taught to be one of the main contributing factors in the development of PNAC [5]. It has been suggested that there are clinical benefits with the use of combining soybean, medium-chain triglycerides, olive oil, and fish oil lipid emulsions, abbreviated as SMOF lipid (SL), as the lipid emulsion [6]. There is still insufficient evidence on which lipid emulsion is ideal for neonates with surgical conditions who require PN. This is because surgical neonates undergo significant immune and metabolic stress from their extra-uterine adaptation, surgical morbidity, operative trauma and the inability to use their alimentary tract [7-10]. This study compares the risk of PNAC developed in surgical neonates receiving IL to their counterparts receiving SL.

**Methods**

A single-centre retrospective study was done between April 2008 and March 2014 at the unit of paediatric surgery at the University of Malaya Medical Centre after obtaining approval from the ethics committee. This study presents the major portion of a larger set of data that had been used for a postgraduate audit prepared by the authors in May 2015.

All surgical patients who received lipid emulsion for at least 21 days were selected and then challenged against the inclusion and exclusion criteria. Of note, the change from IL (INTRALIPID, Fresenius Kabi) to SL (SMOFLIPID, Fresenius Kabi) in the study’s institution took place in April 2011, thus the dates represent the 3 years of IL usage and 3 years of SL.

**Inclusion and Exclusion Criteria:**

Sophisticated criteria are set to ensure equality of conditions and eliminate the factors that may invariably affect the results. These criteria are as follows:

1. Patients receiving PN with at least 2.5 /kg/day of lipid emulsion for a minimum of 21 days were included. In other words, only patients receiving significant lipid emulsion are included.

2. During the studied period of 21 days on PN, patients on intravenous amino acids less than 2.5 g/kg/day, or their intravenous glucose delivery rate < 9 mg/kg/min were excluded. This, indirectly, refers to minimal alimentary feeding if any.

3. Patients with PN interruption for more than 3 days were excluded, whereas those with interruption of 3 continuous or sporadic days were included as long as the total actual days of PN is at least 21 days. This
criterion is mainly meant to eliminate the patients with severe sepsis and its influence on the development of PNAC [11] as the severity of the infection is difficult to quantify.

4. Patients with primary liver diseases, tumours involving the liver, and inborn errors of metabolism were excluded.

5. Only patients who have normal levels of conjugated bilirubin (CB) before the initiation of PN were included. Normal CB level is defined to be less than 9 umol/L [12].

6. Patients with no records of liver function tests (LFT) at the start point or endpoint were excluded. The starting point is defined as the day of starting PN, whereas the endpoint is the day of completion of 2 g/kg/day or more for 21 days. The LFT is accepted if it is recorded on the day or up to 2 days before the starting point and after the endpoint.

PNAC is defined as CB greater than 26 umol/l [12-13]. Since the main aim is to study PNAC in patients on IL vs. those on SL, the presence and severity of PNAC were studied after the completion of 21 days. The severity of PNAC is gauged by the elevation of CB and gamma-glutamyl transferase (GGT).

An independent t-test or chi-square (when applicable) is used to accommodate for concomitant factors when comparing the two groups, which included gender, age, weight, diagnosis, initial bilirubin levels, initial GGT levels, fasting period, numbers of PN interruption days and total grams of lipids received over 21 days.

**Results**

Out of 113 patients receiving PN for at least 21 days, 67 were included. Of these 67 patients, 35 patients were in the IL group whilst 32 patients were in the SL group. In the excluded group of 46 patients, 21 patients had PN interruption of more than 3 days (16 of them were on IL). The reason for the interruption in 19 of them was sepsis. Records were missing in 12 patients, whilst the rest of the excluded patients were scattered among the other exclusion criteria (13 patients).

The analysis of the parameters of the included patients showed that there is no statistical significance between the two groups (IL and SL). Hence, we can safely assume that the key difference between the group on SL and the ones on IL is the type of lipid emulsion. Table-01 and Table-02 summarize the analytical characteristics of both groups.

After 21 days of being on >= 2g/kg/day of lipid emulsion, the cumulated incidence of PNAC in the IL group was 57% compared to 22% in the SL group. The relative risk (RR) of PNAC in the SL group compared to the IL group is 0.38, and the absolute risk reduction (ARR) is 35.27% with 95% confidence interval (CI): [13.50%, 57.04%]. Meanwhile, the RR of PNAC in the IL group compared to SL group was 2.61 with an odd ratio (OR) of 4.76 with 95% CI:[1.62, 13.92].
Patients with PNAC were studied further for the rise of CB and GGT. The elevation of CB and GGT was about 50% less in the SL group compared to the IL group. This difference in the rise proved to be statistically significant for CB, however, it was not significant for GGT elevation.

The approximate number of days required to develop PNAC in the patients who developed it was later by around 2 days in the SL group vs the IL group, but this difference was statistically not significant. Of note, the practice in the study centre is to do biweekly LFT for patients on PN, thus the occurrence of PNAC is approximate with a margin of +/- 2 days hence this data cannot be interpreted accurately. The results are summarized in Table-03

To validate the ARR of SL in the view of the presence of prematurity, a subgrouping was done (full-term vs. premature neonates) and both ARR and OR were calculated for each subgroup. Although a close figure of ARR was resulted (33.52% in premature vs. 36.59% for term neonates), the ARR in the premature subgroup failed to prove statistical significance. The same applies to the OR of IL compared to SL. The aforementioned subgrouping results are detailed in Table-04.

Discussion

The first formulation of the intravenous fat emulsion was in 1961 and soybean oil emulsion has been commercially available under the trade name Intralipid (IL) [13]. IL contains mainly polyunsaturated fatty acids and particularly linoleic (omega-6) fatty acids (about 55%) which in turn contribute to the pro-inflammatory profile of IL. It also contains small amounts (about 8%) of α-linolenic (omega-3) fatty acids. The proportion of omega-6 in addition to the abundance of phytosterols in IL is considered the main contributor to the development of PNAC [14,15].

To curb this serious issue, there was a shift to fish oil-based lipids (such as Omegaven, Fresenius Kabi). This has no phytosterols and contains long-chain polyunsaturated omega-3 fatty acids (55%) in the form of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both with anti-inflammatory capacity. Omegaven was used as a rescue therapy for patients with PNAC and many authors demonstrated that it does not only prevent PNAC but can also reverse it, even in severe forms [16-20].

A mix-based emulsion was suggested as a balanced lipid emulsion and the commonest one is SMOFlipid (SL) [Soy lipid 20%, Soybean oil 30%, Medium chain triglycerides (MCT) 30%, olive oil 25%, and Fish oil 15%]. This composition was chosen to decrease a load of omega-6 polyunsaturated fatty acids, other changes are the inclusion of MCT to provide additional rapidly available energy, part of the polyunsaturated fatty acids being replaced with monounsaturated fatty acids (oleic acid or omega-9) and the omega-3 polyunsaturated fatty acids is increased.

The reduction of PNAC in patients receiving SL compared to IL was demonstrated by many authors over the past decade [21-24]. This study is unique because it discusses PNAC in surgical neonates whose physiology is significantly stressed due to extra-uterine adaptation, surgical conditions, operative trauma and the inability to use the alimentary tract [7-10]. Thus, this study is unique in that it looks at patients...
and the effects of different lipid emulsions, in a group at high risk of developing PNAC, and there is yet no data about the incidence of PNAC in surgical neonates on SL. In this study, precise selection criteria were used to ensure that the comparison between IL and SL is made with near-equal conditions to eliminate the impact of other confounding variables.

The response to multi-stressors in surgical neonates explains the higher incidence of PNAC in both groups (57% in IL vs. 22% in SL) compared to the published incidence (about 20% in IL and 10% in SL) where a mix of patients with surgical and non-surgical conditions are considered [25,26]. Prematurity adds up another burden on these surgical neonates, hence an even higher incidence was encountered in this study (64% in IL and 31% in SL). Numerous studies have discussed the incidence of PNAC in surgical neonates on IL and reported 36% to 68% [27-30]. Yet, to date, there is no explicit report of the incidence of PNAC for surgical neonates on SL and, fortunately, it was possible to report in this study (22% in general, 31% in premature and 16% in full-term).

This study found that about one-third of surgical neonates were spared from developing PNAC (ARR 35%) when using SL compared to IL. Although this finding was almost the same in full-term and premature neonates, the benefit of SL over IL has not been statistically significant in the latter. In addition, the use of IL carries about 5 folds risk of PNAC compared to SL (OR 4.76, P=0.0044). Similarly, this risk failed to be statistically significant in surgical premature neonates (OR 4.05, P=0.0880).

The rise of CB in patients on SL with PNAC was found to be nearly half of its figure when on SL (34 vs. 66 umol/l respectively) and this difference was statistically significant (P=0.0093). However, the rise in GGT, which could be a better indicator of the long-term significance of intrahepatic cholestasis [31], failed to prove statistical significance when comparing patients with PNAC on IL compared to their counterparts on SL (P=0.0582). The number of days on PN required to develop PNAC was also statistically insignificant (P=0.1965) between patients on IL compared to those on SL.

These results confidently show better outcomes with the use of SL, but on the other hand, we are unable to show any statistical significance of improved outcomes with SL vs IL in surgical premature neonates. The established safety and efficacy of pure omega-3 lipid emulsion (like Omegaven) [16-20, 32-35] makes it appealing, the authors believe, as an upfront starting choice rather than being used as a rescue therapy to treat PNAC. This is because lipid emulsion in surgical neonates should be directed to aid in ‘cooling down’ the response to stress rather than concerned about the sufficiency of essential fatty acids (if any). This is particularly during the first few weeks of life in the perioperative period. However, if PN is required for a longer term, SL could be introduced when the inflammatory and metabolic systems are under less strain.

Limitations

This study does not consider factors such as fasting time, surgical diagnosis and sepsis as co-contributors of PNAC since the focus was on a well-controlled comparison between PNAC in patients on
IL compared to those on SL. The recommendation for Omegaven as a first-line choice of lipid for PN in surgical babies remains an evidence-based choice and deserves further study.

**Conclusion**

The incidence and severity of PNAC are less in surgical neonates on SL compared to their counterparts on IL. However, these benefits are unclear in premature surgical neonates. The risk of PNAC in surgical neonates remains the highest, thus consideration of pure fish-oil-lipid as the first line is recommended.

**References**


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23. Rayyan M, Devlieger H, Jochum F, Allegaert K. Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a


### Tables

#### Table-01.

<table>
<thead>
<tr>
<th>Gender (Male: Female)</th>
<th>IL</th>
<th>SL</th>
<th>Statistical Significance (P Value)</th>
</tr>
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<tr>
<td></td>
<td>19:16</td>
<td>14:18</td>
<td>0.3888</td>
</tr>
<tr>
<td>Mean Age for full-term neonates in days (SD)</td>
<td>8.81 (2.84)</td>
<td>8.00 (2.45)</td>
<td>0.3354</td>
</tr>
<tr>
<td>Mean Weight for full-term neonates in Grams (SD)</td>
<td>2447 (460)</td>
<td>2586 (409)</td>
<td>0.3164</td>
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<tr>
<td>Mean Age for premature neonates in weeks (SD)</td>
<td>32.00 (2.15)</td>
<td>32.46 (2.30)</td>
<td>0.5942</td>
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<tr>
<td>Mean Weight for premature neonates in Grams (SD)</td>
<td>1515 (494)</td>
<td>1490 (370)</td>
<td>0.8804</td>
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#### Table-02.

<table>
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<th>Diagnosis</th>
<th>IL</th>
<th>SL</th>
<th>Statistical Significance (P Value)</th>
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<tbody>
<tr>
<td>Necrotising Enterocolitis</td>
<td>12</td>
<td>10</td>
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<tr>
<td>Gastroschisis</td>
<td>8</td>
<td>10</td>
<td></td>
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<tr>
<td>Proximal Small Bowel Ostomy</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Short Bowel Syndrome (SBS)</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Complex Congenital Diaphragmatic Hernia</td>
<td>7</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Patients with PNAC (%)</td>
<td>Days to PNAC* (SD)</td>
<td>Mean of CB Elevation (SD)</td>
<td>Mean of GGT Elevation (SD)</td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------</td>
<td>--------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>IL</td>
<td>20 (57.1%)</td>
<td>14.60 (2.52)</td>
<td>65.85 (38.34)</td>
</tr>
<tr>
<td>SL</td>
<td>7 (21.8%)</td>
<td>16.14 (2.54)</td>
<td>34.43 (18.33)</td>
</tr>
</tbody>
</table>

* error margin - 2 days.

### Statistical significance (P value)

<table>
<thead>
<tr>
<th>Statistical significance (P value)</th>
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<tbody>
<tr>
<td>0.0028</td>
</tr>
<tr>
<td>0.1965</td>
</tr>
<tr>
<td>0.0093</td>
</tr>
<tr>
<td>0.0582</td>
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<tr>
<td>0.0085</td>
</tr>
<tr>
<td>0.0044</td>
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</table>

**Table-04**
<table>
<thead>
<tr>
<th>Total Number of patients</th>
<th>Patient with PNAC (%)</th>
<th>ARR of SL vs. IL [95% CI]</th>
<th>OR of IL vs. SL [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature on IL</td>
<td>14</td>
<td>9 (64.2%)</td>
<td><strong>33.52%</strong> [-1.97%, 69.01%]</td>
<td>4.05</td>
</tr>
<tr>
<td>Premature on SL</td>
<td>13</td>
<td>4 (30.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-term on IL</td>
<td>21</td>
<td>11 (52.3%)</td>
<td><strong>36.59%</strong> [9.66%, 63.52%]</td>
<td>5.8667</td>
</tr>
<tr>
<td>Full-term on SL</td>
<td>19</td>
<td>3 (15.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>