

# 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

**Background:** Parenteral nutrition-associated cholestasis (PNAC) is a significant concern in high-risk surgical neonates, contributing to morbidity and prolonged hospitalization. This retrospective observational study aimed to investigate the impact of different lipid emulsions on the incidence and severity of PNAC in this vulnerable population while controlling for concomitant factors.

**Material and methods:** A cohort of 67 surgical neonates was included, with 35 receiving Intralipid<sup>®</sup> (IL) and 32 receiving SMOFlipid<sup>®</sup> (SL). Rigorous inclusion criteria were applied to ensure comparability between the groups, focusing on the type of lipid emulsion as the main difference and selecting patients with prolonged fasting, limited oral intake, and significant PN reliance. The cumulative incidence of PNAC, absolute risk reduction (ARR), odds ratio (OR), and the effect on specific liver function tests, such as conjugated bilirubin (CB) and gamma-glutamyl transferase (GGT), were evaluated.

**Results:** The SL group exhibited a significantly lower incidence of PNAC compared to the IL group (22% vs. 57%,  $p=0.0057$ ), highlighting the potential protective effect of SL against PNAC development in surgical neonates. Subgroup analysis revealed a lower incidence of PNAC in full-term neonates receiving SL compared to IL (16% vs. 52%,  $p=0.0219$ ), while the difference did not reach statistical significance in premature neonates. Furthermore, SL was associated with a marked reduction in the rise of CB levels compared to IL (34 vs. 66  $\mu\text{mol/l}$ ,  $p=0.0093$ ), indicating a potential hepatoprotective effect.

**Conclusions:** This study emphasizes high-risk surgical neonates' susceptibility to PNAC. The incidence of PNAC exceeded reported rates in lower-risk neonates, highlighting their unique challenges. Although SL reduced PNAC risk compared to IL, the absolute rate remained high and of questionable benefit in surgical premature neonates. These findings prompt further investigation into the optimal lipid emulsion for this vulnerable population, weighing the benefits of SL against potential drawbacks.

**Keywords:** High risk surgical neonates, Intralipid, SMOF lipid, PNAC

## Introduction

Parenteral Nutrition (PN) has been a transformative intervention in neonatal care, enabling the survival of malnourished infants facing challenges in gastrointestinal function due to various medical, traumatic, or surgical conditions [1]. Comprising essential macronutrients like carbohydrates, proteins, and lipids, PN provides vital energy, fostering growth and facilitating healing. Among these constituents, lipids stand out for their high caloric density, offering approximately 10 kilocalories per gram.

The evolution of intravenous fat emulsions in neonatal care has been marked by significant advancements. The initial formulation, Intralipid® (IL), introduced in 1961, predominantly comprises soybean oil, notably rich in pro-inflammatory linoleic acid (omega-6 fatty acid) along with a small amount of  $\alpha$ -linolenic acid (omega-3 fatty acid). This composition has been linked to the development of Parenteral Nutrition Associated Cholestasis (PNAC) [2,3]. PNAC is known to be a challenging condition associated with PN administration, leading to significant morbidity [4,5]. In response to this concern, there has been a shift towards employing fish oil-based lipids like Omegaven®, which is devoid of phytosterols and primarily consists of anti-inflammatory long-chain polyunsaturated omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Omegaven® has shown promise not only in preventing but also in reversing PNAC, even in severe cases [6-11]. Another promising option is SMOFlipid® (SL), a balanced lipid emulsion composed of various components including soybean oil, medium-chain triglycerides (MCT), olive oil, and fish oil. It aims to reduce the proportion of omega-6 fatty acids, provide readily available energy through MCT, replace some polyunsaturated fatty acids with monounsaturated fatty acids (oleic acid or omega-9), and augment the content of omega-3 fatty acids [12].

Nonetheless, the optimal lipid emulsion for neonates, particularly those undergoing surgical interventions and necessitating prolonged PN support amid extended fasting periods and limited oral intake, remains a subject of inquiry. Surgical neonates face heightened immune and metabolic stress due to the exigencies of extra-uterine adaptation, surgical procedures, and the inherent challenges in utilising their gastrointestinal tract [13-16]. This study endeavours to scrutinise the risk of PNAC development in surgical neonates, particularly those belonging to a distinct high-risk population characterised by prolonged fasting and predominantly reliant on PN [17]. Within this high-risk cohort, the study further intends to compare PNAC outcomes between individuals receiving IL and SL emulsions.

## Method

A single-centre retrospective observational study was conducted between April 2008 and March 2014 at the unit of paediatric surgery at the University of Malaya Medical Centre, following approval from the Medical Ethics Subcommittee. This study represents a portion of a larger dataset used for a postgraduate research project 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.

The study's inclusion and exclusion criteria were meticulously devised to establish uniform conditions and mitigate variables that might introduce bias into the outcomes. These criteria have been specifically tailored to encompass solely those high-risk surgical neonates who rely on PN for an extended duration, experience prolonged fasting periods, and have limited oral intake over a 3-week period [17,19]. The following criteria were employed:

1. Patients receiving PN with at least 2g /kg/day of lipid emulsion for a minimum of 21 days were included. In other words, only patients receiving significant lipid emulsion for 3 weeks were included.
2. Patients on intravenous amino acids less than 2.5 g/kg/day, or their intravenous glucose delivery rate is less than 9 mg/kg/min were excluded too. This, indirectly, includes only the patients with minimal alimentary feeding (if any).
3. Patients who experienced a 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 aimed to exclude the patients with severe sepsis since it does influence the development of PNAC [18,19] to a variable degree that is difficult to quantify.
4. Patients with primary liver diseases, tumours involving the liver, cyanotic cardiac defects and inborn errors of metabolism were excluded.
5. Only patients who had normal levels of conjugated bilirubin (CB) before the initiation of PN were included. Normal CB level is defined to be less than 9  $\mu\text{mol/L}$  [20].
6. Patients without liver function tests (LFT) at the start point or endpoint, with a margin of  $\pm 2$  days, 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.

PNAC was defined as a CB level greater than 26  $\mu\text{mol/L}$  [20,21]. The primary objective of the study was to investigate PNAC in patients receiving IL compared to those receiving SL. The presence and severity of PNAC were evaluated after completing 21 days of PN with a lipid dosage of 2 g/kg/day or higher. The severity of PNAC was assessed by analysing the elevation of CB and gamma-glutamyl transferase (GGT), using an independent t-test for comparison.

Between-group comparisons of concomitant factors, such as age, weight, initial bilirubin levels, initial GGT levels, fasting period, number of PN interruption days, and total grams of lipids received over 21 days, were conducted using an independent t-test. Fisher's exact test was employed for categorical variables (presence of PNAC, gender and diagnosis). To compare IL with SL, the study calculated the PNAC odds ratio (OR) and absolute risk reduction (ARR) with their corresponding 95% confidence intervals (95% CI). The significance level was set at 0.05 and the aforementioned statistical analysis was performed using IBM SPSS (Statistical Package for the Social Sciences) version 20.

## Results

A total of 67 out of 113 patients who received the target PN for at least 21 days were included in the study. Of these, 35 patients were in the IL group, and 32 patients were in the SL group. The remaining 46 patients were excluded due to various reasons: 21 patients had PN interruption of more than 3 days (16 of them were on IL), with sepsis being the most common reason for interruption in 19 cases. Additionally, records were missing for 12 patients, and the rest of the excluded patients did not meet the inclusion criteria (13 patients).

There were no statistically significant differences between the IL and SL groups in terms of gender, age, weight, diagnosis, age at surgery, initial levels of CB and GGT, amount of lipids received, or number of PN interruption days. Therefore, the main distinguishing factor between the IL and SL groups was the type of lipid emulsion used. Table-01, Table-2 and Table-03 summarise the analytical characteristics of both groups.

**Table-01:** The Comparative Characteristics of Surgical Neonates Receiving SMOFLipids vs. those on Intralipids.

	IL	SL	P Value
Male: Female	19:16	14:18	0.4664
Mean Age for full-term neonates in days when PN was initiated (SD)	8.81 (2.84)	8.00 (2.45)	0.3354
Mean Weight for full-term neonates in Grams (SD)	2447 (460)	2586 (409)	0.3164
Mean Age for premature neonates in weeks when PN was initiated (SD)	32.00 (2.15)	32.46 (2.30)	0.5942
Mean Weight for premature neonates in Grams (SD)	1515 (494)	1490 (370)	0.8804
Mean Age at main surgery in days (SD)	9.69 (4.19)	8.84 (3.44)	0.3746

**Table-02:** The Categorical Diagnosis for Patients on Intralipid and their counterparts on SMOFLipid (2X5 Fisher's Exact Test revealed  $P= 0.9452$ ).

Diagnosis	IL	SL
Necrotising Enterocolitis	12	10
Gastroschisis	8	10
Proximal Small Bowel Ostomy	4	4
Short Bowel Syndrome (SBS)	4	3
Complex Congenital Diaphragmatic Hernia	7	5
<b>Total</b>	<b>35</b>	<b>32</b>

**Table-03:** The Comparative Characteristics of the Received PN with their statistical analysis.

	IL	SL	P Value
Patients with PNAC	20	7	0.0057
Mean Days to PNAC (SD)	14.60 (2.52)	16.14 (2.54)	0.1965
Mean Total Grams of Lipid in g/kg/21days (SD)	50.74 (3.05)	49.45 (3.47)	0.1110
Mean Fasting Period in Days (SD)	10.46 (4.13)	11.06 (3.53)	0.5228
Mean Initial CB in umol/l (SD)	5.91 (1.96)	5.84 (1.99)	0.8842
Mean of CB Elevation (SD)	65.85 (38.34)	34.43 (18.33)	0.0093
Mean Initial GGT in IU/L (SD)	42.460 (19.18)	41.44 (20.27)	0.8332
Mean of GGT Elevation (SD)	176.70 (125.29)	94.71 (76.93)	0.0582

As depicted in Table-02, the common theme of these surgical conditions was the inability to use the gut sufficiently, coupled with the anticipated prolonged period of fasting before gut utilisation could begin. For example, in gastroschisis, feeds failed to advance due to poor gut motility. In complex congenital diaphragmatic hernia, a substantial duration was required to stabilise patients prior to surgery. In proximal ostomy or short gut syndrome, the high output of stool restricted the advancement of feeds. In premature neonates with surgical necrotizing enterocolitis, it took time for them to stabilise and recover perioperatively.

Throughout the investigated three-week timeframe, each patient in both groups underwent a singular major surgical intervention tailored to their documented diagnosis. Additionally, three patients in the SL group and five patients in the IL group underwent a supplementary procedure under general anaesthesia for the establishment of central venous access within the same period.

After 21 days of receiving at least 2 g/kg/day of lipid emulsion, the cumulative incidence of PNAC was 57% in the IL group and 22% in the SL group. This difference was statistically significant ( $p=0.0057$ ). The ARR of PNAC in the SL group compared to the IL group was 35.27% with a 95% CI of [13.50%, 57.04%]. The OR of PNAC in the IL group compared to the SL group was 4.76 with a 95% CI of [1.62, 13.92]. Both the ARR and OR were statistically significant based on their respective 95% CIs.

Further analysis of patients with PNAC revealed that the elevation of CB and GGT was approximately 50% lower in the SL group compared to the IL group. This difference was statistically significant for CB ( $p=0.0093$ ), but not for GGT elevation ( $p=0.0582$ ).

The time required for the development of PNAC was approximately 2 days longer in the SL group compared to the IL group, but this difference was not statistically significant ( $p=0.1965$ ). It should be noted that the timing of PNAC occurrence was approximate ( $\pm 2$  days) due to the frequency of liver function tests performed in the study centre.

To assess the significance of PNAC and compare the ARR of SL and OR of IL in the presence of prematurity, a subgroup analysis was performed. Surgical neonates were divided into two groups: full-term and premature. The results of this subgrouping are shown in Table-04.

**Table-04:** Parenteral Nutrition Associated Cholestasis (PNAC) in Surgical Premature Neonates versus Term Neonates.

	Total Number of patients	Patient with PNAC (%)	P Value	ARR of SL [95% CI]	OR of IL [95% CI]
Premature on IL	14	9 (64.2%)	0.1283	33.52%	4.05
Premature on SL	13	4 (30.7%)		[-1.97%, 69.01%]	[0.81, 20.20]
Full-term on IL	21	11 (52.3%)	0.0219	36.59%	5.86
Full-term on SL	19	3 (15.7%)		[9.66%, 63.52%]	[1.30, 26.32]

In the premature subgroup, both IL and SL showed a higher incidence of PNAC compared to full-term neonates. However, there was no statistically significant difference between IL and SL ( $p = 0.1283$ ). Conversely, in the full-term subgroup, the incidence of PNAC was lower, and a significant difference was observed between IL and SL ( $p = 0.0219$ ).

The ARR of the subgroups showed very close figures (33.52% for premature and 36.59% full-term), but in the premature subgroup, it did not reach statistical significance as the 95%CI included the null value [-1.97%, 69.01%]. In contrast, the ARR remained significant in the full-term subgroup. Similar trends were observed for the OR of IL. In the premature subgroup, the OR was 4.05 with 95%CI [0.81, 20.20], indicating no statistical significance as the CI included 1. In the full-term subgroup, the OR was 5.86 with 95%CI [1.30 to 26.32], suggesting a statistically significant effect.

## Discussion

This study revealed a significantly higher incidence of PNAC in both groups (IL: 57%, SL: 22%) compared to published rates, underscoring the vulnerability of high-risk surgical neonates.

Several studies conducted in the past decade have demonstrated a decrease in the incidence of PNAC in patients receiving SL compared to IL [12,22-24]. However, these studies included both surgical and non-surgical patients as a whole. The objective of our study was to specifically investigate PNAC in high-risk surgical neonates, as they experience additional stress due to extra-uterine adaptation, surgical conditions, operative trauma, and the inability to utilise the alimentary tract sufficiently for an extended period [13-16]. This study is noteworthy as it examines the impact of different lipid emulsions in a high-risk group susceptible to PNAC [17,19], unlike previous studies that included non-surgical and older patients or mixed surgical patients (high-risk and low-risk). Moreover, there is currently a lack of data regarding the incidence of PNAC in high-risk surgical neonates receiving SL. Therefore, our study aimed to provide valuable insights by employing meticulous selection criteria to ensure a precise comparison between IL and SL while minimising the influence of other confounding variables.

Our findings revealed a 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), which considers a mix of patients with different risk categories [25,26]. This can be attributed to the response of surgical neonates to multiple stressors. The incidence of PNAC was further elevated in premature neonates (64% in IL and 31% in SL), emphasising the additional burden of prematurity. Previous studies have discussed the incidence of PNAC in surgical neonates receiving IL, reporting rates ranging from 36% to 68% [27-30]. However, there is a lack of explicit reports on the incidence of PNAC in surgical neonates receiving SL, particularly high-risk patients. Our study successfully reported the incidence of PNAC in high-risk surgical neonates receiving SL; 22% in general, 31% in premature and 16% in full-term.

The study demonstrated that SL significantly reduced the risk of PNAC in surgical neonates compared to IL, with just above one-third of surgical neonates spared from developing PNAC (ARR 35%). Although this finding was consistent in both full-term and premature neonates, the benefit of SL over IL did not reach statistical significance in the latter. Additionally, the use of IL carried a five-fold higher risk of PNAC compared to SL, but this risk was not statistically significant in surgical premature neonates.

In terms of biochemical markers, the rise in CB, a marker of PNAC, was significantly lower in patients receiving SL compared to IL. However, the increase in GGT, which is indicative of the long-term significance of intrahepatic cholestasis [31], did not reach statistical significance.

The duration of PN needed for PNAC development did not significantly vary between IL and SL recipients. This suggests that the choice of lipid emulsion may not solely dictate the onset of PNAC in this distinctive neonatal group. It's noteworthy that only pure fish oil lipids have shown efficacy in delaying, treating, or potentially reversing PNAC [6, 11].

Overall, our results provide strong evidence for the favourable outcomes associated with the use of SL compared to IL in surgical neonates. Nevertheless, the absolute rate of PNAC remained high in this high-risk group. Moreover, it's important to note that we did not observe enhanced outcomes with the use of SL as compared to IL in surgical premature neonates. Considering the established safety and efficacy of pure omega-3 lipid emulsions, such as Omegaven® [6-11, 32-35], the authors propose that it could be a preferred initial choice rather than a rescue therapy for treating PNAC. Particularly during the perioperative period in the early weeks of life, the focus of lipid emulsion therapy should be on modulating the inflammatory response to stress rather than solely ensuring sufficient essential fatty acids. When the inflammatory and metabolic systems are under less strain, SL could be considered an appropriate and balanced choice.

## Limitations

Several limitations should be considered in our study. While we implemented rigorous inclusion and exclusion criteria, there might still be residual confounding. Additionally, the sample size, especially when stratified by gestational age, was relatively small, limiting the statistical power to detect significant differences. Although there have been no major changes in the care of patients receiving PN over the past decade, the fact that data was collected 10 years ago, may also introduce variability due to nuances changes in clinical practices. Furthermore, PNAC assessment relied on biochemical markers, which may not fully capture the clinical spectrum and severity of the condition. Including additional diagnostic criteria could have provided a more comprehensive evaluation. Lastly, our study focused specifically on comparing IL and SL and did not include other lipid emulsions, which might limit the generalizability of our conclusions to other interventions or lipid choices.



## Conclusion

While our study underscores the potential advantages of employing a balanced lipid emulsion like SL in high-risk surgical neonates, caution is warranted. Despite its demonstrated benefits, particularly in reducing the risk of PNAC, this advantage did not extend to surgical premature neonates in our analysis. This prompts a critical reevaluation of SL as the definitive choice. Future research, incorporating larger cohorts and prospective methodologies, is imperative to validate these findings and pinpoint the optimal lipid emulsion for this vulnerable population. Additionally, long-term studies assessing the impact of lipid choices on neurodevelopmental outcomes and other sequelae of PNAC in surgical neonates will be instrumental in shaping clinical decisions.

## Conflict of Interest

The authors declare no conflict of interest.

## Acknowledgement

Not applicable

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