Parenteral Nutrition Support for the Infant and Parenteral Nutrition Associated Liver Disease: Prevention and Management with Fish Oil Containing Emulsions

Introduction

The use of parenteral nutrition (PN) has given new hope to families of infants who are unable to receive adequate calories enterally due to prematurity, decreased bowel length, or functional intestinal disorders. PN allows for life saving nutrition support for the preterm infant and due to the immaturity of the gastrointestinal tract, there is a lack of tolerance for full enteral feeding.[1] The use of PN is associated with major complications including increased risk of sepsis, intestinal atrophy, and increased vulnerability to inflammatory stimuli, thrombosis, liver dysfunction and eventual failure. Parenteral nutrition associated liver disease (PNALD) manifests at varying degrees ranging from mild cholestasis, severe cholestasis, portal hypertension, and end stage liver disease and some require liver transplantation for survival. PN lipid emulsions have been found to be the causative variable for PNALD. Lipids are essential for the growth and development of infants, especially in neurological development and elimination from the diet could pose detrimental effects for growth and neurocognitive development. This report will review the role of long-term parenteral lipid emulsions in the management of PNALD in infants and children.

Lipid nutrition in the infant

While in utero, lipids are obtained from the maternal diet and transferred through the placenta to the fetus in the form of long chain polyunsaturated fatty acids (PUFA).[2] Approximately 90% of the fetal fat mass is deposited in the final trimester.[3] The placenta preferentially transfers docosahexaenoic acid (DHA) over other fatty acids, which further

implicates the physiologic importance of DHA in the developing fetus.[4] In the third trimester of pregnancy the maternal-fetal transfer of DHA increases, with the deposit of DHA in fetal tissues doubling from 35-40 weeks gestation and alpha-linoleic acid (ALA) and linoleic acid (LA) levels in the infant brain decrease.[2] The fetal liver has very limited capacity to form DHA from ALA, due to limited availability of the enzyme needed for this reaction.[5]

Post birth, the neonate must obtain DHA from the inefficient conversion of ALA to DHA or preferentially the diet. This is particularly challenging for the preterm infant who has had less time in the uterus to accumulate fat stores in the last trimester where uptake is highest.[2] The preterm infant has limited adipose tissue reserves and rely on dietary sources for growth and development. Maternal breast milk provides 20% of the total amount of DHA that was being transferred in the placenta and varies depending on the maternal diet. Infant formulas containing varying amounts of DHA depending on the formula.

Without dietary lipids, infants and children which are dependent on PN will develop essential fatty acid deficiency (EFAD). EFAD manifests with dermatitis, hair loss, hepatosteatosis, and failure to thrive.[6] Biologically EFAD is defined as a triene: tetraene ratio greater than 0.2.[7] A balanced intake of fatty acids is the preferential way to prevent EFAD. At least 10% of total energy must come from PUFA, and 2% - 4% of calories from LA.[8] Close monitoring of the pediatric patient on PN and a low-fat diet must be maintained throughout care to prevent the development of EFAD.

For many years in the United States, the only FDA approved lipid emulsion was derived from soy bean oil. The soy oil lipid emulsion (SOLE) is rich in n-6 PUFA and low in n-3 PUFA. The

DHA and ARA content of SOLE are 0.2% of the total fatty acids, which is below the recommended amounts for a preterm infant.[9] It was found that the serum fatty acid content of very low birth weight infants receiving SOLE for greater than 28 days had a significant decrease in their levels of DHA and ARA.[10] The direct impact of this loss is unknown, although the first weeks of life are supposed to be a time of great gains in PUFA stores. Providing lower than the recommended amounts of DHA and ARA to infants receiving PN can contribute to low growth rate and neurological development deficit.

PN Lipids in the Pathology of PNALD

The Pediatric Intestinal Failure Consortium reported a 74.4% incidence of PNALD within their infant cohort, 22% of the patients required a liver transplant, and 25% mortality over a 2-year period.[11] SOLE has been found to be a major contributor to the manifestation of PNALD. The high level of phytosterols present in SOLE accumulate and disrupt bile acid homeostasis and cholestasis develops. [12] SOLE is high in Omega-6 PUFA which form pro-inflammatory eicosanoids such as prostaglandins and thromboxanes and leukotrienes. [13] Both the relative high ratio of pro-inflammatory mediators to anti-inflammatory mediators, the high level of phytosterols and immunosuppressive properties in SOFL contribute to the development of PNALD.

Substitution of PN Lipid for the Treatment of PNALD

Changing the source of lipid from SOLE to an emulsion containing fish oil has been found to relay beneficial effects on infants and children with PNALD or at risk for PNALD.[14-17] Diamond et al., performed a randomized control trial comparing SMOFlipid containing soybean oil (30%),

medium-chain triglycerides (MCTS) (30%), olive oil (25%), and fish oil (15%) in 11 children with short bowel syndrome and severe PNALD with Intralipid (SOFLE) for 12 weeks. The children who received SMOFlipid had a lower conjugated bilirubin than those receiving Intralipid (mean difference -59 µmol/L; P= 0.03), and they were more likely to have a decrease I serum bilirubin to 0 µmol/L than those in the Intralipid group over the entire period (HR, 10.6;95%;P=0.03).[14]

Skourliakou et al., performed a prospective observational study with infants at gestational age 23-26 weeks and birth weight less than 2500 g with one group receiving SMOFlipid and the other group receiving Intralipid. The group receiving the SMOFlipid saw a decreased incidence of bronchopulmonary dysplasia by 5.6% in the SMOFlipid group and 22.7% in the Intralipid group (P=0.012).[15] For the infants with moderate to severe bronchopulmonary dysplasia significant differences remained at 3.7% vs 16% SMOFlipid and Intralipid respectively (P=0.042).[15]

Nandivada et al., preformed a prospective study on children with intestinal failure associated liver disease (IFALD) examining the outcomes in the children requiring long-term PN and fish oil lipid emulsions therapy. There was a total of 215 patients with IFALD and 30 requires PN and fish oil lipid emulsion therapy for at least 3 years. None of the patients have reported deaths, required transplantation or developed EFAD.[16] The biochemical markers of liver disease normalized within the first year of therapy of therapy, with a long-term stable growth rate. [16]

Muhammed et al., examined the effect on PN-associated jaundice of changing from Intralipid to SMOFlipid in a retrospective cohort of 17 children. The mean bilirubin in the

SMOFlipid group was 143 µmol/L vs 91 µmol/L in the Intralipid group at onset. By 6 months' time, 5 of the 8 children on SMOFlipid had a resolution of jaundice and 2 of 9 had a resolution in the intralipid group.[17] The median bilirubin fell by 99 µmol/L in the SMOFlipid group but increased by 79 µmol/L in the Intralipid group (P=0.02).[17] These studies demonstrate the direct effect on liver functioning which SMOFlipids can help modulate in the pediatric and premature patients.

Conclusion

Infants, predominately premature infants, have distinct nutritional needs for proper growth and neurological development. The preferential usage and uptake of lipids is paramount for this period in life. Patients have a higher risk for PNALD and sepsis due to dependence on PN. The first generation of PN lipid emulsions are 100% soy oil based, Intralipid. The high amount of SOLE is rich in n-6 PUFA, an inflammatory agent and high in phytosterols which accumulate in the liver and possibly confer damaging long-term effects. Heterogenous lipid emulsions from a mixture of plant, fish, MCT, and olive are best associated with positive outcomes on PNALD. These lipid emulsions best mimic the manner which fatty acids are consumed in the diet from a variety of sources, and relate to positive health outcomes.

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