Editorial

Total Parenteral Nutrition-associated Cholestasis: Prematurity or Amino Acids?

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Immaturity of the gastrointestinal tract in very-low-birth-weight infants (<1500 g) (VLBW) precludes substantive nutritional support from enteral nutrition. Therefore, nearly all these infants are supported with parenteral nutrition (PN). In addition, PN has revolutionized the outcome for neonates and infants with intestinal failure either from congenital abnormalities or extensive gastrointestinal surgery. From a nutrition point of view, the liberal use of PN has been a huge success particularly in the VLBW infants.

Aggressive nutrition is a concept being proposed by neonatal nutritionists and is supported by recent studies.[1,2] Theoretically, this means that the transfer from fetal to extrauterine life should proceed with minimal interruption of growth and development.

Amino acids administered from the first hours of life with a goal of providing fetal nutrient delivery rates to the neonate as soon as possible is a cornerstone of this strategy. This is key to avoid the period of early neonatal malnutrition. Several controlled studies have shown the efficacy and safety of amino acids initiated within the first 24 hours of life.[3–7] There were no recognizable metabolic derangements including hyperammonemia, metabolic acidosis, or abnormal aminograms.

A strong argument for the early aggressive use of amino acids is the prevention of ''metabolic shock''. Concentrations of some key amino acids begin to plunge in the VLBW infant from the minute the cord is cut. This metabolic shock may trigger the starvation response, of which endogenous glucose production is a prominent feature. Irrepressible glucose production may be the cause of the so-called glucose intolerance that often limits the amount of energy that can be administered to the VLBW infant. It makes sense to smooth the metabolic transition from fetal to extrauterine life. Withholding PN for days, or even hours, means sending the infant unnecessarily into a metabolic emergency. Thus, the need for PN may never be more acute than right after birth. It is noteworthy that Rivera et al. made the surreptitious observation that glucose tolerance was substantially greater in the group receiving early amino acids; early amino acids may stimulate insulin secretion, which is consistent with the notion that forestalling the starvation response improves glucose tolerance.[7]

As with most therapies in neonatal intensive care, there are risks and complications. In this issue, Wright et al. discusses the increased incidence of PN-associated cholestasis (PNAC) in infants receiving two different pediatric amino-acid formulations.

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The etiology of PN liver disease is unknown and is likely to be multifactorial. Many studies have noted the close relationship among the development of PNAC and birth weight, duration of PN, surgery, sepsis, days on PN before refeeding, and ECMO.[8–11]

The increased incidence of PNAC in premature infants suggests that the development of disease may be related to immaturity of the neonatal liver. It is known that in premature infants the total bile salt pool is reduced. There is both diminished hepatic uptake and synthesis of bile salts as well as reduced enterohepatic circulation compared with full-term infants or adults.[12] Sulfation, which is an important step in the solubilization of toxic bile salts such as lithocholic acid, is also deficient in the fetus and neonate.[13] Therefore, it is likely that the liver and biliary system of the premature infant is more susceptible to toxic damage of any kind.[14,15]

Animal studies have implicated amino acids in the production of cholestasis; whereas studies in human neonates suggest a direct effect of amino-acid infusions on the hepatocyte canalicular membrane.[16] Previously, PN for preterm infants involved the administration of ''general purpose'' amino-acid solutions designed to meet the needs of adult patients. However, preterm neonatal protein requirements are not ideally approximated by these formulas.[17] Furthermore, these general-purpose PN formulations, when administered to preterm infants, are reported to produce abnormal plasma amino-acid profices.[18–22] These abnormalities are probably related to the immaturity of several enzymatic pathways in the preterm infant.[6]

Two intravenous amino-acid formulations specifically designed for infants and young children are currently marketed in the United States. Trophamine (Kendall-McGaw Laboratories, Irvine, CA) is designed to produce plasma amino-acid concentrations approximating those of the healthy, breast-fed, term infant.[23] Aminosyn-PF (Abbott Laboratories, North Chicago, IL) is designed to produce plasma amino-acid concentrations within a composite normal range identified in breast-fed infants and in infants fed general-purpose amino-acid solutions[24–29] Clinical studies comparing these neonatal amino-acid solutions with various general purpose formulations raise concerns about the safety of elevated plasma concentrations of phenylalanine, methionine, and glycine, as well as efficacy questions centered on low plasma concentrations of tyrosine, taurine, cyst(e)ine, and the branched chain amino acids observed in neonates receiving solutions designed for adults. Adamkin et al.[30] in a multicenter study compared the two pediatric intravenous amino-acid solutions in preterm infants and found the rate of weight gain, nitrogen balance, and nitrogen retention to be similar. Seven-day plasma aminograms for both solutions also compared favorably with those from enterally fed preterm infants in the literature.[30] However, it did not address specifically the issue of cholestasis, although liver function tests were similar after the 7 day infusion. Forchelli et al.[31]

reported that the two pediatric amino-acid solutions were similar in the incidence of PNAC observed in 70 infants <1 year who received PN for at least 14 days. Now, Wright et al. report PNAC developing more quickly as well as more severe and prolonged with Aminosyn-PF vs trophamine in a retrospective review.[32]

The prevention or reversal of PNAC is the second cornerstone of aggressive nutrition, the early initiation of enteral feedings. Early enteral feeding maintains the integrity of the intestine, promotes better immune responses, and diminishes bacterial translocation. The gallbladder is stimulated to empty and bile salt metabolism becomes more normal.

As with all therapies in neonatal intensive care, we must remain vigilant and continue to re-evaluate our progress as well as failures. Is it prematurity or the amino-acid solution? Only time will tell. Staying aggressive with nutrition remains a good idea.

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