Neonatal nutrition: a brief review

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Background: **With increasing survival of extremely premature infants, emphasis is now focused on the quality of these survivors' lives. Possibly the most important factor in the premature's ability to survive in the NICU and thrive is the ability to replicate *in utero* growth through enteral and parenteral nutrition.**

Data Sources: **Current literature and review articles were retrieved from PubMed and personal files of the authors.**

Results: **The use and complications of the various components of total parenteral nutrition (TPN) were reviewed. The composition of appropriate enteral feeds for the premature was reviewed as was the difficulties associated with the establishment of adequate enteral feeds in the premature infants.**

Conclusions: **Early initiation of amino acids in TPN and timely increases in the components of TPN can improve the caloric intake of prematures. Enteral feeds, particularly of breast milk, may be started within the first few days of life in all but hemodynamically unstable prematures. Newer lipid preparations show promise in reversing the hepatic damage of TPN associated cholestatic jaundice.**

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Introduction

Over the past number of years there has been increasing survival of extremely small premature infants. With increasing survival, there has been an increased emphasis on the quality of the NICU graduate's life. The ultimate goal for growth of the infant in the NICU is replication of *in utero* growth. Unfortunately this has been extraordinarily difficult to accomplish, particularly in the smallest infants. Due to the immaturity of the premature's gut, it is often difficult to achieve full enteral feeds in a timely fashion. In addition, mother's breast milk is not sufficient to allow for *in utero* growth of the extremely premature infant.

The ability of total parenteral nutrition (TPN) to adequately meet a premature's nutritional needs has improved steadily over the past number of years. Unfortunately it is still difficult to meet *in utero* growth accretion with strictly parenteral nutrition. In addition there are several complications of parenteral nutrition that can cause severe problems for the premature. The aim of this brief article is to review some of the current concepts surrounding the use of TPN to achieve optimal growth, and also to briefly review some of the challenges involved in giving prematures adequate enteral calories and nutrients to match *in utero* growth parameters. Lastly we will review the complications of long-term parenteral nutrition.

Amino acid

Several studies have shown that a protein deficit early in the neonatal period is an important contributor to poor growth, particularly in extremely low birth weight (ELBW) infants. The goal of postnatal nutrition in premature infants is replication of intrauterine growth and nutrient accretion. This goal remains elusive particularly for ELBW infants due to their high rate of protein turnover and catabolism during the first several weeks of life. As the rate of protein breakdown correlates inversely with gestational age, the rate of protein loss in ELBW infants is twice that of term infants.[1] Numerous studies have shown that negative nitrogen balance in sick premature infants who received glucose alone can be reversed with an amino acid intake

of 1.1-2.5 g/kg per day given early postnatally (Fig.).[2] Early infusion of amino acid appears to be associated with greater energy intake due to altered glucose metabolism resulting from increased insulin secretion.[3]

Poindexter, in a study for the National Institute of Child Health and Development (NICHD) Research Network, demonstrated that 3 g/kg of amino acid in the first five days of life in premature infants was associated with significantly better outcomes at 36 weeks postmenstrual age and less suboptimal head growth at 18 months chronologic age.[4] Although other studies have also shown that early parenteral amino acid is correlated with improved protein accretion, and long-term correlated with better growth and neurodevelopment outcomes, there is still reluctance to provide early amino acid to ELBW infants. The main concerns cited are safety and toxicity in a sick ELBW infant with immature renal function. Metabolic acidosis, hyperammonemia and hyperaminoacidemia that were associated with first-generation amino acid solutions are no longer observed with current higher quality protein mixtures.[5] Ridout et al[6] did not find a correlation between amino acid intake and blood urea nitrogen in the first days of life in ELBW babies. te Braake et al[7] concluded that a high-dose of amino acid (2.4 g/kg per day) introduced to VLBW infants within two hours after birth was as safe as a stepwise increase in amino acid intake, and resulted in an anabolic state.

The efficiency of protein retention during parenteral nutrition is approximately 70%. Based on this assumption and the proven benefits of early amino acid intake in limiting protein catabolism, it is reasonable to recommend 2.5-3.0 g/kg per day of amino acid intake directly after birth in premature infants. Parenteral protein of 3.5-4.0 g/kg per day may be required in ELBW infants to maintain endogenous stores, taking into account accretion goals and the rate of protein loss in the neonatal period.

Carbohydrate

In utero, the fetus' glucose utilization matches the umbilical glucose uptake;[8] hence, there is no need for either glycogenolysis or gluconeogenesis. This changes immediately upon birth. The extremely premature infant has not had the opportunity to store much glycogen; and while the stress response of extremely premature birth leads to an epinephrine surge that promotes gluconeogenesis, there is usually a delay in glucose production that leads to hypoglycemia. In the term infants, glucose utilization is 3-5 mg/kg per minute. Utilization in the premature may be as high as 8 mg/kg per minute.[8] The exact definition of both hypoglycemia and hyperglycemia has remained problematic. However, it seems prudent to maintain a premature infant's blood glucose between 40-50 mg/dL and 150 mg/dL.[9] This necessitates the initiation of an intravenous glucose infusion at a rate of roughly 6 mg/kg per minute in the premature immediately following birth.

Hyperglycemia is quite common in the extremely premature infant during the first few days of life. It is most commonly caused by low insulin levels due to defective proinsulin processing, and relative insulin resistance due to the stress response.[10] Treatment can be accomplished either by decreasing the infusion rate, decreasing the glucose concentration or initiating an insulin infusion. Since the basal metabolic requirements of a premature are roughly 60 kcal/kg per day,[11] the dextrose concentration should not be decreased to less than 5% due to concerns about insufficient calories and infusion of a significantly hypo-osmolar solution.

Severe hyperglycemia in the extremely premature infant has been associated with a number of significant morbidities including sepsis, intraventricular hemorrhage, retinopathy of prematurity and ultimately death.[12] A number of studies compared the effectiveness of continuous insulin infusion with reduction in dextrose concentration.[11] Overall they found that with

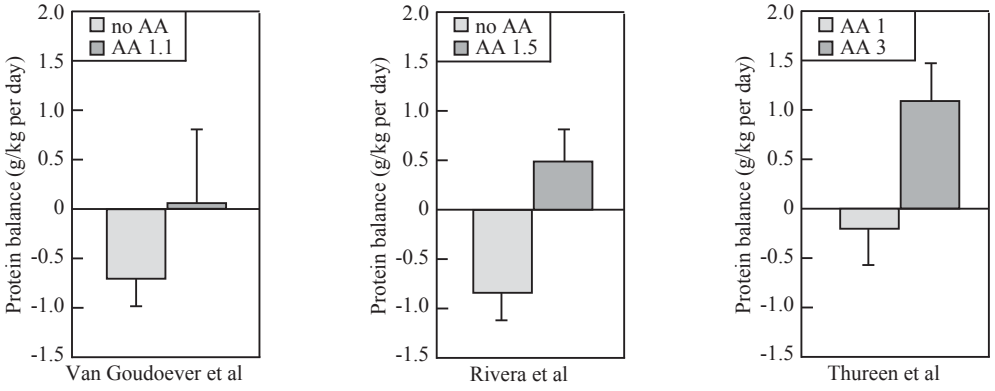

Fig. Protein balance in response to intravenous amino acid administration in ELBW infants in early postnatal life (Cited from Donne et al[2]).

careful monitoring of glucose levels, early insulin therapy improves glucose control with few episodes of hypoglycemia and better caloric delivery to the infant.

In contradistinction to the use of insulin to manage hyperglycemia early in life, many centers will use insulin once an infant is well established on parenteral nutrition solely to increase caloric intake and hasten growth.[13,14] Not only has this been shown to result in no net protein gain by the infant, but a substantial increase in lactic acid with metabolic acidosis was demonstrated.[15] Given that little is known about the quality of weight gain artificially induced by insulin, this practice can not be recommended.

In summary, a glucose infusion of 6 mg/kg per minute should be started on all premature infants upon admission to the nursery. This should be gradually increased to 10 mg/kg per minute over the first week of life. The infant's blood glucose level should be maintained between 50-120 mg/dL. Should the infant become hyperglycemic early on, an insulin infusion (0.01-0.1 units/kg per hour) should be started rather than decreasing the dextrose concentration to less than 5%.[9] Lastly there is no evidence supporting the aggressive use of insulin in the growing premature infant to try to provide additional calories.[16]

Lipid

Intravenous lipids provide a source of essential fatty acids to parenterally fed infants, in addition to providing a calorie dense source of nutrition. The exact composition of the lipid solution varies by manufacturers. The most commonly used lipid formulation in the United States, intralipid, uses soybean oil as a base, although liposyn also contains safflower oil. The main fat components are long chain triglycerides of oleic, palmitic, linoleic and stearic acid.[17] Different formulations are available in Europe, including some that use medium chain triglycerides.

Starting intravenous lipid in very low birth weight (VLBW) infants at an early age has the advantage of providing a source of essential fatty acids, as well as supplying non-carbohydrate calories. Essential fatty acid deficiency can develop in as few as three days in extremely premature infants. Only 0.5-1.0 g/kg per day of intravenous fat emulsion is required to prevent essential fatty acid deficiency.[18] Lipid infusion may be safely started on day 1 of life at 0.5-1.0 g/kg per day and may be increased by up to 1 g/kg per day to a maximum of 3-4 g/kg per day.[19] Endothelial lipoprotein lipase is the enzyme essential for hydrolyzing the lipid particles of the solution. Infants born at <28 weeks gestation have decreased levels of lipoprotein lipase, making triglyceride lipid clearance more difficult than in more mature infants. Triglyceride levels should be followed and lipid infusion temporarily discontinued if the triglyceride level exceeds 150-200 mg/dL.[19]

There have been concerns over the products of lipid metabolism contributing to the development of bronchopulmonary dysplasia (BPD). However, further trials, as well as a randomized controlled trial and meta-analysis did not show any difference in rates of BPD between infants given intravenous lipid soon after birth and infants in whom intravenous lipid administration was delayed.[20] Lipid emulsions are typically given as a 20% solution, since it has less phospholipid emulsifier than the 10% solution. This emulsifier tends to combine with cholesterol to form a by-product that interferes with triglyceride clearance.[17]

There have been alternate lipid infusions proposed that differ in composition from current solutions. A recent review paper summarized several *in vitro* and *in vivo* studies comparing olive oil to soybean oil based intralipid preparations.[21] Olive oil solutions contain decreased concentrations of n-6 polyunsaturated fatty acid which has been noted to adversely affect leukocyte recruitment. Olive oil also contains α-tocopherol, a naturally occurring antioxidant. In addition, large amounts of linoleic acid can impair synthesis of several n-3 long-chain fatty acid derivatives, including eicosapentaenoic and docosahaexaenoic acid. N-3 fatty acids have important effects on the retina and brain.[22,23] Olive oil-based infusions are well tolerated, and may offer advantages for immune function and decreased oxidative stress in the VLBW infant, who is already at risk for invasive infections, as well as oxidative lung injury.

Intralipid solutions are an integral part of parenteral nutrition for the VLBW infant, supplying essential fatty acids as well as a carbohydrate independent source of calories. Future clinical studies will help to better delineate the optimal composition of the lipid solution administered.

TPN complications

Although TPN is a necessary component of providing nutrition to the VLBW neonate, there are several complications that are associated with its administration, especially with a prolonged use.

Prolonged TPN therapy frequently necessitates the placing of a central intravenous catheter, largely secondary to the caustic nature of high concentration TPN. Central catheters carry several risks, including nosocomial infections, as well as more infrequent complications such as vascular thrombosis and cardiac tamponade.[24] The risk of nosocomial infections can be reduced by proper aseptic

technique when placing the catheter as well as following proper dressing care techniques.[25]

TPN associated cholestasis (TPNAC) has long been recognized as a metabolic complication of chronic TPN administration. It is characterized by intracanalicular and intracellular cholestasis. The incidence ranges widely, with 8%-50% of ELBW infants showing signs of biochemical cholestasis after 2 weeks of TPN therapy. The incidence increases with increasing duration of TPN administration, approaching 90% of infants who receive TPN for more than 90 days.[26] The incidence is higher in infants who never receive enteral nutrition, and can progress to hepatic fibrosis and liver failure. The pathophysiology of TPNAC is still incompletely understood, but is felt to be multifactorial in etiology. Systemic risk factors include the overall immaturity of the neonatal liver as well as inflammation resulting from repeated infections. Caloric excess during TPN administration has been shown to lead to steatosis in adults, leading to hepatic injury and cholestasis. Specific amino acid components of the TPN solution have been implicated in some animal models with the development of cholestasis.[26]

Recent studies have focused on soybean oil based lipid solution as possibly being causative of TPNAC. Phytosterols in soybean oil can be damaging to the biliary tract and disrupt bile flow.[27] Based on animal studies showing reversal of TPNAC when the research subjects were given a fish oil base lipid preparation, a clinical study was performed on infants with short bowel syndrome who developed TPNAC while receiving soybean oil-based lipid emulsions. These infants were given fish oil based lipid emulsions, and compared to a historical cohort that received soybean oil-based emulsions only. The fish oil group was found to have a significantly shorter time to reversal of cholestasis compared to the soybean oil group (9 vs. 44 weeks).[28] Proposed mechanisms include the absence of phytosterols as well as decreased pro-inflammatory properties of the n-3 fatty acids in fish oil emulsion.[29]

Treatment for TPNAC is focused toward transitioning to enteral feeds as soon as possible. Other interventions include ursodeoxycholic acid, a bile acid used in adult cholestatic liver disease. Its efficacy in treating and preventing TPNAC is controversial, as studies have not consistently shown benefit.[30,31]

Although TPN can provide adequate nutritional support in the form of glucose, protein, and lipid, parenteral nutrition solutions cannot provide enough calcium and phosphorus to meet the needs of growing VLBW infants. These infants may develop demineralized bone disease, referred to as osteopenia of prematurity. This is the result of decreased new bone formation as well as increased bone turnover.[32]

Enteral feeding

Feeding the low birth weight (LBW) preterm infant poses a unique challenge due to his gastrointestinal dysfunction and limited maturation. Optimal early nutrition is critical for growth, long-term outcome and decreased morbidities.[9,33] The goal is to achieve a growth rate similar to *in utero* fetal growth: 15-20 g/kg per day which is the equivalent to the rate of weight gain during the third trimester, 0.5-0.8 cm/wk in head circumference and 0.8-1.1 cm/wk in length, which requires 120 cal/kg per day enterally.[34,35] Infants with BPD may require higher caloric intake (130-150 cal/kg per day) because of increased work of breathing.[34]

Attempts should be made to begin enteral feedings as soon as possible.[36] Minimal enteral nutrition or trophic feeding is highly recommended to "prime" the gastrointestinal tract with very low volume feedings. It stimulates gut hormones and promotes structural and functional intestinal maturation, decreases indirect hyperbilirubinemia and decreases cholestatic jaundice.[35] Early low volume feedings can result in improved feeding tolerance and a shorter hyperalimentation course, better weight gain and improved bone mineralization. Even sick VLBW infants can be started on small trophic feedings (2-20 ml/kg per day) of human milk or premature formula as early as 1-8 days of life, if hemodynamically stable, and continue for several days. Advancement to full enteral feedings depends on the infant's clinical condition and tolerance, and may be increased by 10-20 ml/kg per day in infants with increased risk for necrotizing enterocolitis (NEC) or faster (20-40 ml/kg per day) in larger babies.[35]

Human milk is the preferred source of enteral nutrition for all infants because of its better digestion and absorption, improvement in host defense, and improved neurodevelopmental outcomes.[33-35,37] Significantly fewer complications such as NEC occur in infants fed with human milk. It is highly recommended to use human milk fortifier for ELBW infants to assure adequacy of human milk and to avoid hyponatremia, hypoproteinemia, osteopenia and zinc deficiency. Human milk fortifier provides additional protein, minerals (Ca, P) and vitamins and is recommended to preterm infants born at less than 34 weeks of gestation with birth weight less than 1500 g or to larger infants with the need to limit volume intake or with suboptimal growth.[37] Preterm infants fed fortified human milk also have shorter hospitalizations and less infection and NEC than infants fed preterm formula. The use of fortifiers is not advocated prior to one week of age. Once an infant has been tolerating breast milk for longer than 1 week, or reached 100 ml/kg per day, it is recommended to add a minimum of 1 packet of

HMF/50 ml of human milk (22 cal/oz), which may be increased up to 3 packs/50 ml (26 cal/oz).[38] Preterm infants with a birth weight of 1800-2000 g also need to be supplemented with iron and vitamin D. There are two types of human milk fortifiers, powder and liquid. If the liquid fortifier is used at 25% of intake, it should be modeled after preterm formula. Powdered fortifiers should only contain the nutrients required for supplementation, and infants receiving protein enhanced expressed breast milk in the first month should be monitored for the effects of protein excess. In all cases, the levels of nutrients delivered by the fortifier and by the representative sample of expressed breast milk fed at appropriate volumes should combine to meet the recommendations of the national pediatric societies or similar scientific organizations, and not exceed the maximum recommended intake for each nutrient.

When human milk is not available, premature formulas will be the primary source of nutrition. Compared to regular term formulas, the premature formulas have higher protein, predominantly a higher content of MCT as the fat, more glucose polymers in addition to lactose, and a higher Ca and P content for better bone mineralization.[34,38] Preterm infants born at more than 34 weeks of gestation and >2.0 kg may feed standard term formula if human milk is not available. Nutrient enriched "Discharge Formula" (22 cal/oz) is also an option. This is more energy and nutrient dense than standard formula and less dense than preterm formula.[34] Monitoring for feeding intolerance is essential, including abdominal examination and daily circumference, gastric residuals, presence of vomiting or abnormal stooling. Gastric residuals should not exceed 25%-50% of the volume fed.

The VLBW infant can be fed either intermittently by bolus every 3-4 hours, given over 15 minutes or longer, or continuously via a pump through an indwelling nasogastric/orogastric or transpyloric tube.[38,39] Continuous feeds may be useful in infants who have not tolerated bolus feedings. Potential problems with any tube feeding include reflux and aspiration, gastric perforation, vagal stimulation and bradycardia, and nasal erosion or palatal groove.

The VLBW infant's nutritional status needs to be assessed daily for weight, fluid and nutrient intake, weekly for length and head circumference and biweekly for biochemical markers such as Hgb, Hct, Ca and P.[38,40] Weight gain of <10 g/day after day 21 of life with caloric intake of ≥24-26 kcal/oz may be an indication for caloric supplements such as MCT oil and polycose.[38]

Conclusion

Ultimately the goal of neonatal nutrition is to try to replicate *in utero* growth patterns. While this is often not possible, particularly in the smallest infants, this article suggests several management strategies to try to reach this goal. Amino acids of as much as 3 g/kg per day should be started parenterally as part of the infant's initial intravenous solution. Glucose at a rate of 6 mg/kg per minute should be started immediately after birth. Severe hyperglycemia should be managed with an insulin infusion if the infant remains hyperglycemic on a 5% dextrose infusion. An intravenous lipid solution of 1 g/kg per day should be started as early as day one or two of life. Enteral feeds, preferably of breast milk, should be started within the first few days of life even in critically ill infants as long as they are hemodynamically stable. The major complication of parenteral nutrition, TPN associated cholestasis, is ultimately treated by advancing enteral feeds. Newer lipid preparations, however, show some promise in reversing the hepatic damage of prolonged TPN.

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