Protein and Neurodevelopment of Preterm Infants

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We have known for years that protein is an essential nutrient. However, the unique role of protein metabolism in growth and Neurodevelopmental outcome is based on much newer data. Research by Patti Thureen, MD, Ekhard Ziegler, MD, Brenda Poindexter, MD, Scott Denne, MD and others has clarified information regarding protein and led to changes in clinical management.

It wasn't so very long ago that we waited a day or two (or perhaps three) to start parenteral nutrition after birth. Even when it was started, parenteral protein was often given at 1 gm/kg/day, advancing by a cautious 0.5 gm/kg/day, eventually reaching a maximum of 2.5 or 3 gm/kg/day. Did we have literature to back up this cautious approach? Not really – but it was dogma. Then "out-of-the-box" articles began to appear suggesting that this approach really wasn't necessary and giving protein earlier would not only be safe, but also result in establishing positive nitrogen balance earlier.[1-13] Patti Thureen's article[12] about giving protein early to sick infants really encouraged a change in practice, because many neonatologists were concerned that a more aggressive approach could do harm to these most fragile infants. Now it is not uncommon for the first IV solution for some infants to be protein and dextrose, given at 2 gm/kg or a "vanilla" basic TPN giving 2-3 gm/kg. Early provision of protein at 2.5 g/kg/day has been shown to be safe and results in positive nitrogen balance in infants undergoing abdominal surgery for gastroschisis soon after birth.[14]

When preterm infants are born, they have very little nutrient storage. Giving IV glucose alone will result in a loss of 1% of the body's protein stores daily. The smaller and more immature the infant is, the greater the protein loss. Infants with respiratory distress syndrome have shown benefit from an early nutrition support with amino acids and enteral feeding. Benefits included: (a) fewer days of mechanical ventilation, (b) fewer days to regain birthweight, and (c) a lower percentage of maximal weight loss.[15] Increasing evidence shows that protein malnutrition affects neurodevelopmental outcome;[16-18] therefore, it is imperative to establish positive nitrogen balance as soon as possible.

Parenteral Protein Intake: Research and Practice

The change in practice has been to start IV protein early instead of late. The safety and benefit of early protein administration for preterm infants (both well and ill) has been determined in many studies.[1-13] Early provision of amino acids stimulates whole-body protein synthesis instead of depressing protein breakdown,[19,20] as well as stimulating albumin synthesis.[21] Lingering concerns among clinicians about early use of protein center on an increase in blood urea nitrogen (BUN), cholestasis, and abnormal newborn screens. With normal renal function, low BUN has been shown to correlate linearly with inadequate protein intake. A high BUN may be a reflection of fluid deficit, but it is not a good marker for protein excess. Higher intravenous amino acid intake in a prospective trial comparing 1 gm/kg/day versus 3 gm/kg/day did not result in a greater degree of acidosis or higher BUN. The higher protein group was in positive nitrogen balance.[11] Another analysis also showed no relationship between BUN and amino acid intake.[22] A study that used 4 gm/kg/day amino acids as compared to 3 gm/kg/day in ELBW infants showed a mean serum BUN of 18.2 (+/- 8.8 mg/dl), the same for both groups in the first day of life without significant acidosis.[13] Jadhav and colleagues looked at the relationship between metabolic acidosis and amino acid intake and did not find a correlation; all of the low-birth-weight infants developed a metabolic acidosis, but it was not correlated to amino acid intake.[23]

The concern regarding an increase in bilirubin is based on an article by Villeisus in 1980, but this article does not illustrate an increase in cholestasis with increasing parenteral protein, only in the rate of rise.[24] Another, more recent article did not find a relationship between protein intake and cholestasis in a group of the most vulnerable preterms (600 to 1,000 gm); therefore, protein should not be limited in these infants.[25] With more recent thoughts regarding the role of soy-based lipids and phytosterols in cholestasis,[26,27] the role of protein in the development of cholestasis is not as compelling. Abnormal newborn screens may be seen with infants on parenteral nutrition, but this pattern is easily recognized and differentiated. The screen can be repeated when on full enteral nutrition.

What are the goals for protein intake? The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition suggests increasing protein to a maximum of 4.5 gm/kg/day, with intakes in the range of 4.0 to 4.5 gm/kg/day. Recommended intakes to deliver protein at fetal delivery rates are listed in Table 1.

Some excess of recommended values is not harmful, but even a small deficit impairs growth.[29] Protein quantity and quality are important and the ideal parenteral amino acid solution is still elusive. TrophAmine, the most commonly used neonatal amino acid solution, is based on the serum amino acid profile of the term 1-month-old breastfed infant. However, the best

Table 1: Recommended Intake to Deliver Protein at Fetal Delivery Rates[28,29]

Week of Gestation	Parenteral Protein Intake
24-25 weeks	3.75-4.0 g/kg/day
27-28 weeks	3.5 g/kg/day
32 weeks	3.2 g/kg/day
Term Infants	2.8-3.0 g/kg/day

Table 2: Enteral Protein Recommendations[29]

Body wt g	Protein g/kg/d	Energy kcal/kg/d	Protein/energy g/100 kcal
500-700	4.0	105	3.8
700-900	4.0	108	3.7
900-1200	4.0	119	3.4
1200-1500	3.9	125	3.1
1500-1800	3.6	128	2.8
1800-2200	3.4	131	2.6

amino acid intake for the growing premature infant may resemble fetal accretion in the second trimester; in this case TrophAmine is deficient in both lysine and threonine.[29] More research is ongoing to devise solutions designed for the premature infant.

In a study of early provision of parenteral amino acids to extremely low-birth-weight (400–1,000g) preterms, a secondary analysis of 1,018 infants was performed to determine whether early protein intake is associated with better growth and neurodevelopmental outcomes.[16] Infants who received 3 gm/kg amino acids within the first 5 days of life (early) and infants who reached 3 gm/kg/day after 5 days of life (late) were compared. Growth was better at 36 weeks for weight, length, and head circumference. At 18 months there was no statistically significant difference in weight, length, or head circumference between the two groups, although significantly more infants in the late group had head circumferences below the 10th and 5th percentiles. Of this group, boys had smaller head circumferences twice as often as girls. At 18 months corrected age (CA), 85% of these infants were seen for developmental testing. Using criteria of the Mental Development Index and Psychomotor Development Index <70, Neurodevelopmental impairment (cerebral palsy, hearing loss requiring amplification and blindness in both eyes) was no different between the groups.[16] Since this study only reports on 18-month CA outcomes, differences may become even more evident when these infants reach school age.

Enteral Protein Intake: Research and Practice

Enteral nutrition may be more effective than parenteral nutrition in promoting protein accretion and reducing protein breakdown.[20,30] Since ELBW infants may not reach full enteral nutrition for weeks, more research is needed to determine if a combination of parenteral and enteral nutrition might lower breakdown and improve protein synthesis better than parenteral nutrition alone.[20] The use of breast milk correlates with improved developmental outcomes at 18 and 30 months of age.[31,32]

Table 2 outlines recommendations for enteral protein intake based on body weight (in grams). However, without manipulation, standard preterm formula or breast milk (see Table 3) does not provide the higher recommended protein. Use of these products alone to provide the recommended protein intake requires higher volume and more calories, which may not be needed. Either a protein supplement is needed, or preterm formulas need to be reformulated.

In a study of very low-birth-weight (VLBW) infants a preterm formula with increased protein content was used.[34] Infants in the higher protein (preterm) formula (3.6 gm/100 cal) group were compared to those on a standard (3.0 gm/100 cal) formula. Nitrogen intake and retention were greater in infants on the higher protein formula, as were weight gain and retinol binding protein, an assay of protein nutriture. There were no signs of protein intolerance.[34] This formula would seem a better way to meet the needs of rapidly growing preterm infants, and also the enteral protein goals mentioned earlier.

An adjustable breast milk fortification method for premature infants using a low BUN as an indicator to increase fortification and protein intake was used by Arslangolo et al.[35] Infants fed by this method had significantly greater weight gain and head circumference growth than infants on standard fortification of breast milk.[35]

Just as NICU care varies for oxygen and ventilator use with variation in morbidity and mortality, differences in growth of preterms from 6 NICUs have been identified.[41] Some NICUs consistently provided more protein and energy to their infants and, not surprisingly, their infants grew better. They found that an additional 1 gm/kg/d of protein translated into an increase in growth velocity of >4 gm/kg/d.[41]

Studies actually document differences in long-term outcomes with changes in protein intake. Alan Lucas and colleagues studied the use of preterm versus

Table 3: Protein Content of Standard Preterm Formula and Breast Milk[33]

Preterm Formula	Protein g/100 cal	Human Milk	Protein g/100 cal
Special Care 30®	3.00	Preterm Mother's milk + 1 pkt to 25 ml Similac Human Milk Fortifier®	2.97
Special Care 24®	3.00	Term Mother's milk + 1 pkt to 25 ml Similac Human Milk Fortifier®	2.58
NeoSure Advance®	2.80	Preterm mother's milk	2.10
Similac Advance®	2.07		

standard infant formula in the first month of life in preterm infants.[17] They found significantly impaired cognitive function at 7 years of age in preterm infants given term infant formula or banked donor breast milk in the first month. The major differences between the formulas are in the protein and mineral content, higher in the preterm formula. Boys were more affected than girls by suboptimal nutrition in this study: boys in the higher nutrient group had a 12-point higher score in verbal IQ. Using MRI, a new follow-up of adolescents from this study has shown an increase in brain volume in the caudal area and higher verbal IQ scores in the high nutrient group.[18] Two follow-up studies of VLBW preterms at 8-9 years[42,43] show a correlation between subnormal head circumference growth and poorer developmental outcome. In the Hack study[40] there was a correlation between subnormal head circumference growth at 8 months and later IQ and scores for receptive language, speech, reading, and spelling even after adjusting for socioeconomic and neonatal risk factors.

Since the critical period of brain growth is in the first 2 years of life, what to feed preterm infants after hospital discharge is also being studied. Cooke has studied premature infants who were, fed a preterm formula until 6 months' postconceptual age. The girls showed no difference in growth but boys fed preterm formula tended to have greater head circumference growth.[36-38] These findings are significant, because outcomes of prematurity for boys are worse than for girls. Embleton[39] uses a protein and calorie deficit model when viewing postnatal nutrition. The deficits are calculated by subtracting the actual intake from the goal intake for infants. This deficit concept has been used by Europeans for making recommendations for postdischarge feeding.[40]

Despite the cited research, there is not universal agreement on the benefit of protein in either early or later nutrition. The study by Clark et al[44] comparing growth with two gradually increased amino acid steps (one leading to high and one leading to lower amino acid content) showed no difference in growth. This study has been subject to much criticism by the community of neonatal protein researchers.[45,46] The meta-analysis by Henderson[47] regarding postdischarge nutrient enrichment flies in the face of many other studies,[48-54] the AAP[48] and more recent ESPGHAN recommendations.[40]

The majority of studies show that earlier, higher protein intake may improve growth, possibly reduce Neurodevelopmental adverse outcomes, and affect brain structure. The first 2 or 4 weeks of life for the premature infant may represent a critical window of growth. During this period, nutrition from protein may have its greatest benefit (as well as adverse effects) if not provided in sufficient quality and quantity.

Conclusions and Recommendations

Perhaps improving the nutrition of premature infants throughout their hospitalization and the first year of life, but particularly in the first 2 to 4 weeks of life, will improve outcomes. Tentative nutrition increases, partially due to the fear of intolerance (parenteral) as well as the fear of necrotizing enterocolitis have prevented advancing the nutritional quality of enteral feeding. Gone are the days when "just anything" at "just anytime" can be given to preterms to meet their protein needs. Recommendations for improving protein intake in this vulnerable population include:

- More "aggressive" rather than tentative use of early, higher-protein parenteral nutrition.
- Consideration of "total nutrition" as a combination of parenteral and enteral nutrition.
- Earlier fortification of human milk (at 100 ml/kg) instead of waiting till full enteral feedings. Some preterms may be able to start feedings with fortified breast milk.
- Later discontinuation of parenteral nutrition until there is adequate enteral intake of protein and calories.
- Formula-fed preterms may be able to: (a) start feeding with 24 calorie formula or (b) transition to 24 calorie preterm formula earlier.
- Increasing the protein content of current preterm formulas.[16,34,35]

As we all learned in our basic nutrition course, protein functions to build and repair body tissues. Certainly research on the impact of protein intake on long-term outcomes needs to continue. "Old" feeding/nutrition practices should be replaced with evidence-based nutrition by all healthcare providers, inpatient and outpatient, who care for preterm infants. ●

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