Early nutritional support for extremely premature infants: what amino acid amount should be given?

Scott C Denne*  
Indiana University School of Medicine, Section of Neonatal-Perinatal Medicine, Riley Hospital for Children, Indianapolis, IN

Consistently providing adequate nutrition to extremely preterm infants remains a clinical challenge. This is especially true in early postnatal life, when support is largely dependent on parenteral nutrition and often complicated by glucose and lipid intolerance.

Large nutritional deficits, in particular protein deficits, can rapidly accumulate in extremely preterm infants. Without amino acid intake, the protein stores of extremely preterm infants are diminished by 1.5%/d, whereas the fetus is accumulating protein at 2%/d (1). Multiple studies have shown that early amino acid intake in very-low-birth-weight infants can improve protein balance and minimize protein deficits (2, 3). A large observational trial showed significantly improved growth outcomes at 36 wk corrected gestational age in extremely-low-birth-weight (ELBW) infants who received at least 3 g amino acids · kg⁻¹ · d⁻¹ before 5 d of life (4). A number of single-site observational trials also reported improved growth outcomes with increased early amino acid delivery to very-low-birth-weight infants (5, 6). Some randomized controlled trials of higher amounts of amino acid intake reported improved growth outcomes in premature infants (7, 8), although some did not (9). Although early parenteral nutrition support appears to be a beneficial clinical strategy, the optimal amount of that support is not fully known.

As reported in this issue of the Journal, Uthaya et al. (10) conducted a blinded randomized controlled trial in very premature infants that examined the effect of an immediate high amount of amino acids (3.6 g · kg⁻¹ · d⁻¹) compared with a lower and gradually increasing amount (1.7 g · kg⁻¹ · d⁻¹ increasing to 2.7 g · kg⁻¹ · d⁻¹ over 2 d) on body composition. With the use of a 2-by-2 factorial design, the study also simultaneously evaluated the effect of a multicomponent lipid emulsion compared with a soybean-only–based lipid emulsion on intrahepatic cellular lipid content.

No differences were detected between the groups in the primary outcomes of nondipose mass for the amino acid intervention and intrahepatic cellular lipid content for the lipid intervention. There were also no significant differences in most of the prespecified secondary outcomes in the 2 interventions. However, the group who received the higher amino acid dose had higher blood nitrogen concentrations and a smaller head circumference at term. The authors conclude that high amino acid intakes should be used with caution in very preterm infants and only in the context of randomized controlled trials.

This was a well-conducted randomized trial that assessed important outcomes and adds to our understanding of nutritional interventions in extremely preterm infants. However, the primary outcomes of the study were negative, and it is important to not overinterpret the significance of the secondary findings.

Although some clinicians regard blood urea nitrogen (BUN) concentrations as a marker of toxicity from protein, there is no evidence to support that view. Modest elevations of BUN show effective metabolism of amino acids that are not incorporated into protein; this metabolic pathway is important in the fetus because amino acids are an important energy source. In addition, BUN reflects not only amino acid intake but also other factors such as hydration status and renal function. A number of studies have shown no significant relation between amino acid intake and BUN in extremely preterm infants in early postnatal life (11, 12). Furthermore, there are data that show no alteration in the aminogram for ELBW infants with BUN concentrations >15 mmol/L (13). In the absence of significant renal dysfunction, there is no evidence that modest elevations of BUN (10–15 mmol/L) have clinical consequence.

The finding of a smaller head circumference in the higher amino acid infusion group is, on the surface, potentially more worrisome. However, a number of considerations make this more likely a chance finding. Previous observational and randomized controlled trials did not find decreases in head circumference in response to higher amino acid intakes (4–9); indeed, a recent randomized controlled trial that used a study design and amino acid intake very similar to the present study showed that the higher amino acid intake resulted in a significant increase in head circumference (8). Despite the small differences in head circumference, Uthaya et al. found no differences in brain volumes between the 2 amino acid groups. Finally, and perhaps most importantly, the head circumferences measured in all groups were just above or below the 50th percentile for head circumference at 40 wk corrected gestational age (14). This was an improvement in head circumference percentile from that measured at birth in all groups. Thus, this secondary finding seems very unlikely to be of clinical significance.

Uthaya et al. did not show a significant increase in lean body mass as a result of a higher initial amino acid intake. It is not

*To whom correspondence should be addressed. E-mail: sdenne@iupui.edu.

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a criticism of this well-conducted study to point out that this result is not surprising. As demanded by study ethics, both groups were provided with excellent nutritional support. Nutrition was delivered within 24 h of birth, and both groups achieved a caloric intake of 50 kcal·kg⁻¹·d⁻¹ on day 1 and 80 kcal·kg⁻¹·d⁻¹ by day 3. Enteral nutrition was begun on day 1, and both groups achieved full enteral intakes by day 12. There appear to be no significant differences in caloric intake between the 2 groups at any point in the study. The difference in protein intake was very small, ~10 g total over the first 3 wk (<0.5 g·kg⁻¹·d⁻¹). Less than 9 g total protein separated the 2 groups through 34 wk corrected gestational age. This difference in protein intake is simply too small to find a significant difference in lean body mass; the study was powered to detect a 200-g difference in nonadipose mass. It is important to note that the growth outcomes of both amino acid groups were fairly good. As previously discussed, head circumferences at term gestational age in both groups were at approximately the 50th percentile. Length percentiles at term were similar to those measured at birth (slightly greater than the 10th percentile), and the average weight at term was at approximately the 15th percentile.

So what are the implications for current clinical care from this valuable study by Uthaya et al.? First, the use of a well-outlined strategy of early parenteral and enteral nutritional support in very preterm infants is feasible and can produce reasonable, if not entirely optimal, growth outcomes. Second, when providing good early nutritional support, higher amounts of early amino acids may not be necessary to achieve reasonable growth outcomes but seem unlikely to be clinically detrimental. Finally, to precisely delineate the optimal amount of early amino acids on important clinical outcomes, very large clinical trials will be necessary.

Currently, there are still a substantial number of neonatal intensive care units that do not have effective procedures to provide early and ongoing nutritional support to extremely preterm infants (15). Until we have more precise information, consistently providing immediate nutritional support with amino acids within the range studied by Uthaya et al. (1.7–3.6 g·kg⁻¹·d⁻¹) along with enteral feedings appears to be the clinical strategy with the best chance of producing reasonable growth outcomes for extremely preterm infants.

The author did not declare any conflicts of interest.

REFERENCES