Targeting 2.5 versus 4 g/kg/day of Amino Acids for Extremely Low Birth Weight Infants: A Randomized Clinical Trial

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Objective To compare the effect of 2.5 vs 4 g/kg/d of amino acid (AA) in parenteral nutrition of extremely low birth weight infants on metabolic tolerance, short-term growth, and neurodevelopment.

Study design One hundred thirty-one infants with birth weight between 500 and 1249 g were randomized to 2.5 (standard AA [SAA] group) or 4 (high AA [HAA] group) g/kg/d AA intake, with equal nonprotein energy. The primary outcome was body size at 36 weeks.

Results One hundred thirty-one patients were randomized and 114 analyzed (58 SAA group and 56 HAA group). Study groups had similar demographics and clinical characteristics. Elevated blood urea (BU >70 mg/dL = BU nitrogen >32.6 mg/dL) occurred in 24% vs 59% ($P = .000$) and hyperglycemia (>175 mg/dL) in 34% vs 11% ($P = .003$) of the SAA and HAA patients, respectively. Body weight, length, and head circumference at 36 weeks and 2 years were similar between groups. *Bayley Scales of Infant and Toddler Development, Third Edition* score was 94 ± 13 in the SAA group and 97 ± 15 in the HAA group ($P = .35$).

Conclusions The HAA group had higher BU levels and better glucose control. An extra 8 g/kg of AA over the first 10 days of life did not improve growth and neurodevelopment. *(J Pediatr 2013;163:1278-82)*.

Early parenteral amino acid (AA) administration has become part of routine care in preterm infants. Several studies have demonstrated the efficacy of early AA provision in reversing the negative nitrogen balance.[1-7] Safety of AA administration is usually measured with biochemical variables such as blood urea (BU), metabolic acidosis, blood ammonia, and plasma AA. None of the studies on early AA provision has demonstrated any significant metabolic alteration, demonstrating that AA administration early after birth is safe and well-tolerated in preterm infants.[2-8] The majority of studies have focused on AA intakes lower than 2.5 g/kg/d.[1-3,7,8] Whether or not AA intakes greater than 2.5 g/kg/d will be well tolerated and will improve growth in preterm infants remain controversial. As a result, there is still a wide variability in clinical practice.

There are 2 randomized clinical trials (RCTs) with the primary objective of comparing solely the impact of different AA intakes commencing on the first day of life.[9,10] Clark et al compared the effect of 2.5 vs 3.5 g/kg/d on short-term growth,[9] and Tan et al assessed the affect of 3 vs 4 g/kg/d on head growth and neurodevelopment.[10,11] Both studies were unable to show significant benefits of 1 extra g of AA during neonatal parenteral nutrition (PN).

The aim of this trial is to compare the effect of 2.5 vs 4 g/kg/d of AA in PN of extremely low birth weight infants (ELBWI) on metabolic tolerance, short-term growth, and neurodevelopment.

Methods

Eligible infants had a birth weight (BW) between 500 and 1249 g and written parental consent. The Polytechnic University of Marche Ethics Committee approved the study. Outborn admitted beyond 24 hours of age and patients with birth asphyxia, life expectancy shorter than 7 days, major congenital abnormalities, and congenital metabolic disorders were excluded. After randomization exclusion criteria were death before discharge, necrotizing enterocolitis, and gastrointestinal surgery.

Randomization was obtained with sealed envelopes using a random permuted blocks within strata protocol. The stratification groups were based on BW: group 1 from 500-749 g, group 2 from 750-999 g, and group 3 from 1000-1249 g.

AA	Amino acid	HAA	High amino acid
Bayley III	*Bayley Scales of Infant and Toddler Development, Third Edition*	NPE	Nonprotein energy
		PMA	Postmenstrual age
BU	Blood urea	PN	Parenteral nutrition
BUN	BU nitrogen	RCT	Randomized clinical trial
BW	Birth weight	SAA	Standard amino acid
ELBWI	Extremely low birth weight infants		

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Although caregivers were aware of the PN group assignment, growth and neurodevelopment were assessed by personnel blinded to treatment assignment.

Primary outcome variables were body weight and the incidence of small for gestational age infants at 36 weeks postmenstrual age (PMA). Secondary outcomes were in-hospital growth performances, such as maximum weight loss, age at regained BW, age at 1800 g, growth velocity from birth to 1800 g, growth velocity from regained BW to 1800 g and from regained BW to 36 weeks PMA, weight, total body length, and head circumference at 36 weeks PMA.

Secondary outcome measures also included metabolic tolerance, assessed by BU, triglycerides, and glucose concentrations, as well as blood pH and standard base excess. The 2-year follow-up included body weight, total body length, head circumference, and neurodevelopment, assessed according to the *Bayley scales of Infant and Toddler Development, Third Edition* (Bayley III).[12]

During admission, body weight was measured daily using a digital infant scale. Head circumference and total body length were measured weekly using a flexible nonstretchable tape and a neonatal stadiometer respectively. Data were prospectively recorded with dedicated software (Neotools; Interactive, Milan, Italy). SDS of body weight, length, and head circumference were calculated using Italian reference growth charts.[13]

During the first 10 days of life, blood glucose measurement as well as blood gas analysis was performed daily; hyperglycemia was defined as 2 consecutive blood glucose measurements greater than 175 mg/dL at least 6 hours apart. BU was measured on PN day 2, 4, and 6. Serum triglycerides were checked on day 4 and 6.

The enteral feeding scheme was the same for the 2 study groups. All patients received minimal enteral feeding from birth to day 7 (8 mL/kg/d for the first 3 days and 16 mL/kg/d from day 4-7); enteral feeding was then increased with daily increments of 8, 12, and 16 mL/kg/d for the 3 birth-weight groups, respectively (see above). Human milk was the first choice, and all mothers were encouraged to express human milk; infants whose mothers did not provide sufficient amounts of human milk received preterm formula in addition to human milk.

PN was initiated immediately after birth as soon as vascular access was established. Patients in the standard AA (SAA) group were planned to receive 1.5 g/kg/d on day 1, followed by increments of 0.5 g/kg/d to a maximum of 2.5 g/kg/d on the third day of life. Neonates in the intervention group (high AA [HAA] group) were planned to receive 2.5 g/kg/d on day 1 and reach a maximum of 4 g/kg/d on day 4. The 2 study groups were designed to give an additional 12 g/kg of AA during the first 10 days of life to the intervention group. Nonprotein energy (NPE), minerals, and micronutrients intakes were identical for the 2 groups; the AA solution was TrophAmine 6% (Baxter Healthcare Corporation, Round Lake, Illinois). Duration of PN was different according to BW categories (it was 24, 18, and 14 days for babies weighting from 500-749 g, from 750-999, and from 1000-1249 g, respectively).

PN was prescribed daily by clinical care staff members according to standard guidelines: glucose was increased from 6-12 g/kg/d from the first to the sixth day of life and lipids from 0.5-2.5 g/kg/d from the first to the fifth day of life. AA intake was reduced based on strict clinical guidelines; BU cut off was set at 70 mg/dL (BU nitrogen [BUN] 32.6 mg/dL) above which the amount of AA was lowered to 2g/kg/d and checked after 24 hours. If serum triglycerides were above 250 mg/dL, the lipid intake was reduced by 1 g/kg/d and checked again after 24 hours; if serum triglycerides reached 400 mg/dL, the amount of lipids was lowered to the minimum intake of 0.5 g/kg/d. Glucose cut off level was set at 175 mg/dL above which glucose intake was lowered to a minimum of 6 g/kg/d. If hyperglycemia still persisted, insulin infusion was started.

Statistical Analyses

During the years 2004-2006, 52% of the infants with BW between 500 and 1249 g had a weight below −2 SD at 36 weeks PMA. We estimated that to reduce the number of infants with a weight below −2 SD at 36 weeks PMA by 50% with alpha at 0.05 and power at 80%, 110 infants were required. We performed an intent-to-treat analysis using SPSS v. 18 (SPSS Inc, Chicago, Illinois). The χ^2 test and ANOVA were used were appropriate.

Results

Between December 2006 and August 2009, 159 neonates were screened and 131 (82%) were enrolled: 67 in the SAA group and 64 in the HAA group. Reasons for nonenrollment were admission after 24 hours of age (n = 10), life expectancy shorter than 7 days (n = 6), birth asphyxia (n = 3), major congenital malformations (n = 7), and inborn errors of metabolism (n = 2). After randomization, 17 patients (9 in the SAA group and 8 in the HAA group) were withdrawn from the study. Reasons for withdrawal were death (n = 5 in the SAA group, n = 4 in the HAA group), necrotizing enterocolitis (n = 2 in the SAA group, n = 2 in the HAA group), and gastrointestinal surgery (n = 2 in the SAA group, n = 2 in the HAA group). Data of 114 patients (58 in the SAA group and 56 in the HAA group) were analyzed. Nonenrolled infants had similar demographic and clinical characteristics of those belonging to the study groups (data not shown).

Protocol Experience

Over the first 10 days of life, the mean difference of AA intake between groups was 8 g/kg (±0.47, P = .000.) (**Figure 1**). By study design, NPE intakes of the first 10 days were almost identical between the 2 study groups (mean NPE intakes over the first 10 days were 49.4 ± 6.6 and 50.4 ± 6.5 Kcal/kg/d for the SAA and HAA groups, respectively, P = .563). There were no differences in the cumulative amount of total milk and calories from birth to 36 weeks PMA, which were 5782 ± 2325 mL/kg for the SAA group vs 6112 ± 2301 mL/kg for the HAA group (P = .453) and 4691 ± 1924 Kcal/kg for the SAA group vs 4995 ± 1942 Kcal/kg (P = .409) for the HAA group. Cumulative human milk