Safety and Efficacy of Early Parenteral Lipid and High-Dose Amino Acid Administration to Very Low Birth Weight Infants

Hester Vlaardingerbroek, MD, PhD[1], Marijn J. Vermeulen, MD, PhD[1], Denise Rook, MD, PhD[1], Chris H. P. van den Akker, MD, PhD[1], Kristien Dorst[1], Josias L. Wattimena[2], Andras Vermes, PharmD, PhD[3], Henk Schierbeek, PhD[1,4,5], and Johannes B. van Goudoever, MD, PhD[1,4,5]

Objective To assess the efficacy and safety of early parenteral lipid and high-dose amino acid (AA) administration from birth onwards in very low birth weight (VLBW, birth weight <1500 g) infants.

Study design VLBW infants (n = 144; birth weight 862 ± 218 g; gestational age 27.4 ± 2.2 weeks) were randomized to receive 2.4 g of AA $kg^{-1} \cdot d^{-1}$ (control group), or 2.4 g AA $kg^{-1} \cdot d^{-1}$ plus 2-3 g lipids $kg^{-1} \cdot d^{-1}$ (AA + lipid group), or 3.6 g AA $kg^{-1} \cdot d^{-1}$ plus 2-3 g lipids $kg^{-1} \cdot d^{-1}$ (high AA + lipid group) from birth onwards. The primary outcome was nitrogen balance. The secondary outcomes were biochemical variables, urea rate of appearance, growth rates, and clinical outcome.

Results The nitrogen balance on day 2 was significantly greater in both intervention groups compared with the control group. Greater amounts of AA administration did not further improve nitrogen balance compared with standard AA dose plus lipids and was associated with high plasma urea concentrations and high rates of urea appearance. No differences in other biochemical variables, growth, or clinical outcomes were observed.

Conclusions In VLBW infants, the administration of parenteral AA combined with lipids from birth onwards improved conditions for anabolism and growth, as shown by improved nitrogen balance. Greater levels of AA administration did not further improve the nitrogen balance but led to increased AA oxidation. Early lipid initiation and high-dose AA were well tolerated. *(J Pediatr 2013;163:638-44)*.

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Malnutrition in humans during critical stages of development has long-lasting negative effects on both growth and neurodevelopment, at least through school age and possibly also into adulthood.[1] In recent decades, multiple studies have demonstrated that early parenteral amino acid (AA) administration (up to 3.0 $g \cdot kg^{-1} \cdot d^{-1}$) is safe, well tolerated, and results in an increased protein synthesis rate and positive nitrogen balance, indicating an anabolic state.[2-8] However, lipid administration has not received similar attention. Lipids are not only fundamental to providing the essential n-6 and n-3 fatty acids necessary for central nervous system development but also supply the dietary energy necessary for the optimal use of AAs for protein synthesis. In most neonatal intensive care units (NICUs), lipids are introduced on the second or third day of life or in very low amounts (0.5-1 $g \cdot kg^{-1} \cdot d^{-1}$) from birth onwards because of concerns about lipid intolerance. However, meta-analyses of early lipid introduction (before day 2) have not shown increased risks of common neonatal morbidities.[9,10]

We describe neonatal growth, safety, and clinical course of very low birth weight (VLBW) infants subjected to nutritional regimens with different intravenous lipid and AA intakes starting soon after birth. We hypothesized that both lipids and greater levels of AA administration from birth onwards would be safe and well tolerated and would result in an improved nitrogen balance.

Methods

Between December 2008 and January 2012, we performed a randomized controlled trial at the NICU of the Erasmus MC–Sophia Children's Hospital in Rotterdam, The Netherlands. The eligible patients were inborn VLBW infants (birth weight <1500 g) with a central venous catheter in place to allow for more concentrated glucose solutions and to restrict total fluid intake. Written informed consent was

AA	Amino acid
ECF	Ethyl chloroformate
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
SGA	Small for gestational age
TG	Triacylglycerol
VLBW	Very low birth weight

From the [1]Division of Neonatology, Department of Pediatrics, Erasmus MC-Sophia Children's Hospital; Departments of [2]Internal Medicine and [3]Hospital Pharmacy, Erasmus MC, Rotterdam, The Netherlands; [4]Department of Pediatrics, Emma Children's Hospital-AMC; and [5]Department of Pediatrics, VU University Medical Center, Amsterdam, The Netherlands

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obtained from the infants' parents before they were included. Exclusion criteria were congenital anomalies, including chromosome defects and known metabolic diseases, or endocrine, renal, or hepatic disorders. The study protocol was approved by the institutional medical ethical review board.

The attending physician included infants within 6 hours of birth by opening a sealed, opaque randomization envelope stratified for weight (<1000 g or 1000-1499 g) and sex. The envelopes were created by a research pharmacist who was not involved in clinical care and were based on a computer-generated block randomization list with variable block sizes that was provided by a statistician. For logistic reasons, the study group randomization was open after inclusion; however, all technicians were blinded for study group randomization throughout the study and the analyses.

The infants received glucose (at least 4.0 $mg \cdot kg^{-1} \cdot min^{-1}$) and 2.4 $g \cdot kg^{-1} \cdot d^{-1}$ of AA (always on stock on the ward) as part of standard clinical care. Immediately after randomization to 1 of 3 groups, the experimental parenteral nutrition was substituted for all infants except those who were allocated to the control group.

The infants in the control group received glucose and AA (2.4 $g \cdot kg^{-1} \cdot d^{-1}$) during the first 2 days of life. Lipids were started on the second day of life at 1.4 $g \cdot kg^{-1} \cdot d^{-1}$ and were increased the following day to 2.8 $g \cdot kg^{-1} \cdot d^{-1}$.

The infants in the AA + lipid group received glucose and AA similar to the control infants (2.4 $g \cdot kg^{-1} \cdot d^{-1}$), but lipids were started soon after birth (starting dose of 2 $g \cdot kg^{-1} \cdot d^{-1}$, next day increased to 3 $g \cdot kg^{-1} \cdot d^{-1}$).

In addition to glucose from birth, the infants in the high AA + lipid group received both high-dose AA (3.6 $g \cdot kg^{-1} \cdot d^{-1}$ from birth onwards) and lipids (a starting dose of 2 $g \cdot kg^{-1} \cdot d^{-1}$, increased the next day to 3 $g \cdot kg^{-1} \cdot d^{-1}$).

All of the groups received the same AA product: Primene 10% (Baxter, Utrecht, The Netherlands). The infants in the control group received Intralipid 20% (Fresenius Kabi, Bad Homburg, Germany). The infants in the intervention groups were randomized to receive either Intralipid 20% or SMOFlipid 20% (Fresenius Kabi). Because the lipid type did not have an effect on our primary outcome, lipid type was not included in the final analyses. In all groups, minimal enteral feeding was initiated on the day of birth and advanced to full enteral nutrition, according to the local protocol. After the third day of life, the nutritional regimen, including enteral feeding, was at the discretion of the attending physician.

Throughout the study, the local protocol was to temporarily lower the parenteral intake of AA when plasma urea concentrations were between 10 and 14 mmol/L (28-39 mg/dL) and to temporarily cease AA administration when plasma urea concentrations exceeded 14 mmol/L (39 mg/dL). Similarly, parenteral lipid intake was temporarily lowered when triacylglycerol (TG) concentrations were between 3 and 5 mmol/L (265-442 mg/dL) and temporarily stopped whenever TG concentrations exceeded 5 mmol/L (442 mg/dL). These guidelines were based on expert opinion.

According to the local protocol, repeated blood glucose concentrations >10 mmol/L (180 mg/dL) were treated with continuous intravenous insulin (starting dose 0.1 $U \cdot kg^{-1} \cdot h^{-1}$) if reducing the glucose infusion rate to a minimal intake of 4 $mg \cdot kg^{-1} \cdot min^{-1}$ was not effective. Baseline characteristics were recorded. The nutritional intake was recorded daily until the infants were on successful full enteral feeding (ie, no parenteral feeding for 2 consecutive days).

Primary Outcome

The efficacy of the intervention was analyzed by quantifying the nitrogen balance on postnatal days 2, 4, and 6. The nitrogen balance was calculated by subtracting the urinary nitrogen excretion from the recorded nutritional intakes (parenteral + enteral), under the assumption that 1 g of AA contains 160 mg of nitrogen. Nitrogen excretion was measured in urine with the use of a CHN elemental analyzer (ANA 1500; Carlo Erba Strumentazione, Milan, Italy). The urine was collected with gauze in the diaper during a 6- to 24-hour period on the study days. After centrifugation at 2800 g for 5 minutes, the urine samples were stored at −20°C until further analysis.

Secondary Outcomes

Hematology and biochemistry data were recorded during the first week of life. Hyperuremia was defined as a urea concentration >10 mmol/L (28 mg/dL), and hypertriacylglycerolemia was defined as a TG concentration >3 mmol/L (265 mg/dL). In a subset of infants with an arterial catheter inserted for clinical reasons, a stable isotope study was performed on day 2 to measure the urea rate of appearance, reflecting the rate of urea synthesis (control group, n = 7; AA + lipid group, n = 9; high AA + lipid group, n = 12). During isotope infusion, no adjustments were made to the nutritional infusions. AA concentrations also were analyzed (control group, n = 11; AA + lipid group, n = 16; high AA + lipid group, n = 17) (**Appendix**; available at www.jpeds.com).

The time needed to regain birth weight, the growth rate during the first 28 days of life, the gain in lower leg length (knemometry)[11] during the first month of life, and growth until discharge home (or until 40 weeks corrected gestational age, whichever occurred first) were measured.[12] The safety of the intervention beyond the first week was monitored based on clinical outcome, that is, survival, duration of hospital stay, and neonatal morbidity. The definitions used for the clinical diagnosis are specified in the **Appendix**.

Statistical Analyses

Power calculation based on an expected increase of the nitrogen balance (primary outcome) by 75 ± 100 mg nitrogen $kg^{-1} \cdot d^{-1}$ on day 2,[4] 30 infants per group were needed (α = 0.05 and β = 0.80). Accounting for expected losses to follow-up and practical limitations in blood and urine sampling, we included 50% more infants per group.

Linear regression analysis was used to calculate a mean length gain (mm/d) for each infant individually. Differences between groups were analyzed with χ^2 tests and a one-way ANOVA with Bonferroni correction for multiple testing, as