Clinical Nutrition 35 (2016) 344–350

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized control trials

Albumin synthesis in very low birth weight infants is enhanced by early parenteral lipid and high-dose amino acid administration☆

Hester Vlaardingerbroek [a, 1], Henk Schierbeek [a, b], Denise Rook [a], Marijn J. Vermeulen [a], Kristien Dorst [a], Andras Vermes [c], Johannes B. van Goudoever [a, b, d, *], Chris H.P. van den Akker [a]

[a] Department of Pediatrics, Division of Neonatology, Erasmus MC – Sophia Children's Hospital, c/o Room SP3433, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands
[b] Department of Pediatrics, Emma Children's Hospital – AMC, c/o Room H7-282, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands
[c] Hospital Pharmacy, Erasmus MC, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands
[d] Department of Pediatrics, VU University Medical Center, c/o Room ZH 9D11, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 2 July 2014
Accepted 29 April 2015

Keywords:
Preterm infant
Parenteral nutrition
Anabolism
Growth
Stable isotopes
Mass spectrometry

SUMMARY

Background & aims: Albumin is one of the most important plasma proteins and plays a key role in many physiologic processes, such as preserving colloid osmotic pressure, scavenging radicals, and binding and transporting bilirubin, hormones, and drugs. However, albumin concentrations are often low in preterm infants during the first days of life.
We hypothesized that early parenteral lipid and high-dose amino acid (AA) administration to very low birth weight (VLBW) infants from birth onwards increases hepatic albumin synthesis rates.
Methods: Inborn VLBW infants were randomized to receive from birth onwards either 2.4 g amino acids/(kg·d) (control group), 2.4 g amino acids/(kg·d) plus 2 g lipids/(kg·d) (AA + lipid group), or 3.6 g amino acids/(kg·d) plus 2 g lipids/(kg·d) (high AA + lipid group). On postnatal day 2, infants received a primed continuous infusion of [U-$^{13}C_6$,^{15}N]leucine. Mass spectrometry was used to determine the fractional and absolute albumin synthesis rates (FSR and ASR, respectively).
Results: In total, 28 infants (median gestational age 27 weeks (IQR 25–28), median birth weight 810 g (IQR 679–998) were studied. The median FSR was 6.5%/d in the control group, 10.6%/d in the AA group, and 12.3%/d in the high AA + lipid group, while the median was 84 mg/(kg·d) in the control group, 138 mg/(kg·d) in the AA group, and 160 mg/(kg·d) in the high AA + lipid group.
Conclusion: A group of VLBW infants given parenteral nutrition containing lipids and high-dose amino acids showed a higher rate of albumin synthesis compared to infants receiving no lipids and standard amounts of amino acids during the first two days of life.

1. Introduction

Albumin, the most abundant plasma protein, accounts for 75–80 % of the maintenance of colloid osmotic pressure in plasma because of its relatively low molecular weight. Albumin is well studied for its role in adult and neonatal physiology that includes many other important functions, such as acid buffering and transport of bilirubin, free fatty acids, uremic toxins, metals, nitric oxide, hormones, and drugs such as antibiotics [1]. In addition, albumin is an important antioxidant because of its specific binding sites for copper ions and its free sulfhydryl group, which can scavenge harmful reactive oxygen species [2]. These functions make albumin of vital importance to the critically ill preterm infant. Several

Abbreviations: AA, amino acid; ASR, absolute synthesis rate; CRIB, critical risk index for babies; FSR, fractional synthesis rate; GMP, good manufacturing practice; MPE, mole percent excess; NICU, neonatal intensive care unit; NOD, non-oxidative disposal; NOLD, non-oxidative leucine disposal; TG, triacylglycerol; VLBW, very low birth weight.

☆ The trial has been registered at www.trialregister.nl, trial number NTR1445, name: Nutritional Intervention for Preterm Infants-2.

* Corresponding author. Emma Children's Hospital – AMC, c/o Room H7-282, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands. Tel.: +31 20 5667729; fax: +31 20 5669683.
E-mail address: h.vangoudoever@amc.uva.nl (J.B. van Goudoever).
[1] Present address: Department of Pediatrics, Emma Children's Hospital – AMC, c/o Room H7-282, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands.

http://dx.doi.org/10.1016/j.clnu.2015.04.019

authors have described an inverse relationship between albumin concentrations and mortality and morbidity, although the cause of the hypoalbuminemia, rather than the low albumin concentrations itself, may be responsible [3,4]. However, exogenous albumin infusion in preterm infants with hypoalbuminemia does not seem to reduce mortality and morbidity [1,5,6]. The endogenous stimulation of albumin synthesis might be more effective. In fetal studies, albumin synthesis seems to be much lower in preterm neonates than in fetuses [7,8], presumably because of postnatal malnutrition or increased stress [9]. Because albumin synthesis rates have been shown to be responsive to parenteral nutrition [8,10,11], it can be speculated that endogenous synthesis can be increased by the optimized administration of amino acids and energy. Therefore, we studied the effect of parenteral lipid administration (energy), with standard and high-dose amino acid administration, from birth onwards on plasma albumin synthesis rates on the second day of life in very low birth weight (VLBW) infants. We hypothesized that the additional amino acids and the calories provided by lipids would improve albumin synthesis rates.

2. Subjects and methods

2.1. Study design and patients

In this randomized controlled trial, we enrolled VLBW infants (birth weight < 1500 g) admitted to the neonatal intensive care unit (NICU) of the Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands between June 2009 and January 2012. Inclusion criteria were: birth weight <1500 g, inborn, both arterial and central venous catheters inserted for clinical purposes, and parental written informed consent. The included infants were a subset of the infants included in a study by Vlaardingerbroek et al. [12,13] determining the safety and efficacy of early lipid (soybean oil or a multicomponent emulsion) initiation with or without additional amino acids from birth onwards. In addition, the metabolism of the amino acids leucine and phenylalanine in this subset of infants was published previously [14]. Excluded were infants with congenital anomalies, including chromosome defects; infants with metabolic diseases; and those with endocrine, renal or hepatic disorders. The study protocol was approved by the institutional medical ethics review board.

The attending physician enrolled infants within 6 h after birth by opening a sealed, opaque randomization envelope stratified by weight (<1000 g or 1000–1499 g) and gender. 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 determined 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.

2.2. Nutritional intervention

As soon as intravenous access was obtained after birth, the infants received glucose (at least 4.0 mg/[kg·min]) and 2.4 g/(kg·d) of amino acids (always on stock in the ward) according to standard clinical protocol. As soon as possible after birth (but not later than 6 h after birth), infants were randomized to one of three groups and the appropriate nutrition regimen was immediately initialized:

2.2.1. Control group

The infants in the control group received only glucose and amino acids (2.4 g/[kg·d]) during the first two days of life. Lipids were not introduced until after the stable isotope study on the second day of life.

2.2.2. AA + lipid group

The infants in the AA + lipid group received glucose and amino acids similar to the control infants (2.4 g/[kg·d]), but lipids were administered from randomization onwards with an initial dose of 2 g/(kg·d) and increased the next day to 3 g/(kg·d).

2.2.3. High AA + lipid group

In addition to receiving glucose from birth onward, the infants in the high AA + lipid group received both high-dose amino acids (3.6 g/[kg·d]) and lipids with an initial dose of 2 g/(kg·d) that was increased the next day to 3 g/(kg·d) from randomization onwards.

All infants received the same amino acid product: Primene 10% (Baxter, The Netherlands). The infants in the intervention groups were randomized to receive either Intralipid 20% or SMOFlipid 20% (both Fresenius Kabi, Germany). Because the lipid type did not have an effect on albumin kinetics, the type of lipid was ignored in the final analyses of this study (Supplemental Tables 1 and 2). Whenever possible, minimal enteral feeding was initiated on the day of birth and advanced to full enteral nutrition in the following days, according to the local protocol.

For safety reasons, the local protocol included the temporary adjustment of the parenteral intake of amino acids when plasma urea concentrations were above 10 mmol/L (28 mg/dL) and adjustment of the parenteral lipid intake when triacylglycerol (TG) concentrations were above 3 mmol/L (265 mg/dL) [12]. If adjustments to parenteral intake were necessary prior to or during tracer infusion, infants were excluded from this isotope study.

2.3. Data collection and analysis

At birth, we recorded sex, birth weight, birth weight *z*-score [15], gestational age based on best obstetric measurement (ultrasound in early pregnancy or last menstrual period), number of prenatal steroid doses (0, 1 or 2), and severity of illness upon entry into the study by means of the Apgar score at 5 min and the Critical Risk Index for Babies (CRIB) score [16]. Actual nutritional intake was recorded.

2.4. Albumin synthesis rate

2.4.1. Tracer infusion

Good manufacturing practice (GMP)-tested, >94% enriched, [U-$^{13}C_6$,^{15}N]leucine was purchased from Cambridge Isotope Laboratories (Andover, MA) and tested for its concentration, purity, sterility and pyrogenicity according to GMP guidelines. [U-$^{13}C_6$,^{15}N] leucine was dissolved in 0.9% saline by the hospital pharmacist after which the solution was filtered (0.2 μm) and sterilized. Tests were performed to ensure the correct identity, concentration, sterility and pyrogenicity.

On the second day of life, each infant received a primed continuous infusion of [U-$^{13}C_6$,^{15}N]leucine (12 μmol/[kg·h]) lasting for 8 h using a Perfusor fm infusion pump (B. Braun Medical B.V., Oss, the Netherlands). The priming dose equaled an hourly dose. After 6, 7, and 8 h of infusion, 0.5 mL of blood was sampled from the arterial catheter. The total amount of blood sampled did not exceed 5% of the patient's estimated total blood volume of 75 mL/kg. Immediately after collection in EDTA-containing tubes, the samples were placed on melting ice and centrifuged (10 min, 3500×G). Plasma was stored at −80 °C until analysis.

2.4.2. Analytical methods

To isolate plasma albumin, samples (50 μL of plasma) were purified by the addition of 400 μL of anti-human serum albumin affinity resin in spin columns (Vivascience – Sartorius Group, Hannover, Germany) and were subsequently eluted. After