



Research Article

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Early Parenteral Protein and Glucose Control in Extremely Low Birth Weight Infants



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Abstract

Background: In the extremely low birth weight (ELBW) population, glucose intolerance and hyperglycemia commonly occur in the first 2 weeks of life. Providing amino acids as soon as possible after birth, will improve glucose homeostasis.

Objective: Assess if the early use of amino acids (<4 hours of life) with the infusion of standardized parenteral formulation was associated with better glycemic control in the first 72h of life in a group of ELBW infants.

Methods: A case control study was undertaken in preterm newborns <1000g who were admitted to the intensive care unit. Cases were eligible if they starting with “early” intravenous amino acid (EA) infusion in the 0 to 4 hours of life. Controls were infants <1000g paired with gestational age and weight who received 10% intravenous glucose at birth (infusion rate 4.5mg/kg/min) followed by “late” initiation of parenteral nutrition with amino acids after 4 hours of life (LA). We compared both groups by the timing of initiation of amino acid management.

Results: A total of 142 infants were included based on timing of amino acid initiation. 71 infants in the EA and 71 infants in the LA. We found an expected difference in the median hours of initiation of amino acids: EA group 1.88±1.5 vs. LA 19.1±6.4h (p 0.001). During the first glucose determination, a lower concentration of capillary glucose was detected in the EA group (84.4±24.4mg/dL vs. 100.4±44.1mg/dL). We found a significant lower proportion of hypoglycemia, hyperglycemia and the need of insulin use in the EA group.

Conclusion: Our results demonstrate that EA initiation is associated with decreased hypoglycemia and hyperglycemia in extremely low birth weight infants.

Keywords: Extremely low birth weight (ELBW); Very low birth weight (VLBW); Insulin-like growth factor one (IGF-1); Special preterm solution (SPS); Early amino acid” (EA); Late amino acid (LA)

Introduction

In the extremely low birth weight (ELBW) population, glucose intolerance and hyperglycemia commonly occur in the first 2 weeks of life. Hyperglycemia is a particular concern since significant hyperosmolar state can cause contraction of the intracellular volume of the brain, which may contribute to intraventricular hemorrhage. A study using continuous glucose monitoring confirmed that as many as 80% of very low birth weight (VLBW) infants experience elevated glucose levels during the first week of life and that the risk of developing hyperglycemia is inversely related to gestational age and birth weight [1].

The mechanism of hyperglycemia in preterm infants is not fully understood but it may relate to both relative insulin resistance and defective islet β -cell function. Providing amino acids as soon as possible after birth, will improve glucose homeostasis. Early

protein intake also affects insulin-like growth factor one (IGF-1) concentrations, and IGF-1 plays an important role in endocrine modulation of growth [2]. IGF-1 lowers blood glucose levels by increasing peripheral glucose uptake and glycogen synthesis as well as suppressing hepatic glucose production [3].

There is evidence that the early protein with higher levels of protein and energy intake of 3.0-3.5g/kg per day in the first days of life has been shown to be well tolerated, safe and effective in improving protein accretion and modulates the endogen insulin synthesis [4]. On the other hand, the use of the standardized neonatal parenteral nutrition formulation can optimize macronutrient intake and improves the efficiency of early protein administration with significant increased amino acids and caloric intakes, and it reduced early weight loss [5-7].

The Instituto Nacional de Perinatología is a tertiary-level hospital where 200 preterm infants born <1000g are attended each year. A case control study was undertaken in order to assess if the early use of amino acids (<4 hours of life) with the infusion of standardized parenteral formulation was associated with better glycemic control in the first 72h of life in a group of ELBW infants.

Methods

Enrolment

Preterm newborns <1000g who were admitted to the intensive care unit during March 2012 through January 2013. Cases were eligible for inclusion on the day they were born starting nutritional management with “early” intravenous amino acid infusion in the 0 to 4 hours of life according to our nutritional guidelines. We used a standardized formulation for initiation based on 80mL/kg/day with protein 2.3g/kg, glucose 4mg/kg per minute, calcium 150mEq/kg/day with osmolarity of 740mOsm/L with the possibility of be administrated by peripheral venous catheterization. We call this solution a “Special preterm solution” (SPS). Preterm newborns with low Apgar score (<6 at 5min), gastrointestinal malformations, genetic syndromes, maternal chorioamnionitis or early sepsis (confirmed by blood culture) fetal acidemia (ph<7.0 or BD>12) or need of vasoactive drugs in 72h of life were excluded from the study.

Controls were infants <1000g born between January 2008 to March 2012 paired with gestational age and weight. According a preset protocol received 10% intravenous glucose at birth (infusion rate 4.5mg/kg/min) without amino acids in the first 4 hours of life followed by “late” initiation of parenteral nutrition with amino acids after 4 hours of life. Both groups were started on trophic feedings (12.5ml/kg/d) with human milk when available or 24kcal premature infant formula.

Outcomes Were compared both groups by the timing of initiation of amino acid management with “early” defined as initiation before 4 hours of life and “late” defined as initiation after 4 hours of life.

We evaluated the outcomes during the first 72h of life and accordingly with our institutional protocol for hyperglycemia management, all the infants with blood glucose values greater than 150mg/dL the glucose infusion was reduced to 4mg/kg/min. Insulin therapy was used for babies already receiving a glucose infusion rate in 4mg/kg/min with persistent blood glucose values greater than 200mg/dL. The starting insulin infusion was 0.01 U/kg per hour and the glucose levels were checked hourly until blood glucose levels between 150 to 200mg/dL were reached. For hypoglycemia we used for definition a plasma glucose concentration <47mg/dL for the first 72 hours of life.

Sample size and analysis

Based on the study from Mahaveer et al. [8] an estimated reduction in the need of insulin for hyperglycemia reported in a previous study from 53% to 26% we used a proportion difference with a power of 0.95 and alpha of 0.025, calculating a sample size of

71 patients for each group. Continuous variables were compared by using Student’s t test for distribution-free quantitative variables; Fisher exact test was used to ascertain significant differences in categorical variables between groups. Significance was defined at p<0.05. OR and 95% CIs as well as medium differences were analyzed. Statistical analysis was performed using the software package SPSS 20.0.

Results

Table 1: Baseline Neonatal characteristics of groups.

	Early amino acids n=71	Late amino acids n=71	P
Birth weight (g)	831±129	846±107	0.477
Gestational age (weeks)	28.3±1.6	28.4±1.4	0.780
Malegender	32 (45.1%)	28 (39.4%)	0.497
Prenatal steroids (%)	45 (63.4%)	55 (77.5%)	0.066
IUGR (%)	21 (29.6%)	24 (33.8%)	0.588
Initiation of amino acid (hours of life)	1.88±1.59	19.1±6.4	0.000

IUGR: Intrauterine Growth restriction (<10th percentile, with Fenton Growth charts) 19.

A total of 142 infants were included based on timing of amino acid initiation. 71 infants in the “early amino acid” (EA) and 71 infants in the “late amino acid” (LA). Neonatal characteristics are shown on Table 1. There were no differences in weight, gestational age, gender, as for prenatal steroids were used in 63.4% of the cases and 77.5% of the controls in our population. IUGR was 29.6% in EA vs. 33.8% in LA without statistical differences (p 0.588). We found an expected difference in the median hours of initiation of amino acids: EA group 1.88±1.5 vs. LA 19.1±6.4h (p0.001). During the first glucose determination, which was performed one hour after the start of intravenous solutions, a lower concentration of capillary glucose was detected in the EA group (84.4±24.4mg/dL vs. 100.4±44.1mg/dL).

Table 2: Glucose level by the timing of the aminoacid initiation.

	Early amino acid N=71	Late amino acid N=71	P	OR (IC 95%)
Hypoglycemia (<47mg/dL)	1 (1.4%)	11 (15.5%)	0.003	12.8
Hyperglycemia (>150mg/dL)	18(25.4%)	37 (52.1%)	0.001	3.2 (1.57, 6.5)
Use of Insuline for hyperglycemia	2 (2.8%)	12 (16.9%)	0.009	7.01 (1.50, 32.6)

In Table 2 we found a significant lower proportion of hypoglycemia in the EA group as well as a significant lower proportion of hyperglycemia and the need of insulin use for managing hyperglycemia. The pattern of insuline-treated hyperglycemia was the same in both groups.

Discussion

Glucose delivery to the fetus occurs at low fetal insulin concentrations and at a rate that reflects energy utilization. Maintaining normal glucose concentrations that match those of the normally growing fetus might be important for neurodevelopment [9]. The purpose of early aggressive nutrition is to reduce the cumulative caloric and protein deficits in acute stage to a minimal degree and hence to prevent extrauterine growth restriction and associated abnormal cognitive and neurodevelopmental outcomes [10].

This study was a quality improvement project to evaluate a change in clinical nutrition practice using historical control subjects. In general, it appears that 2.0g/kg/d of parenteral amino acid administration is sufficient to avoid negative protein balance in all neonatal populations if concomitant catabolic conditions are not present. The introduction of early amino acids as a part of management changes in our unit suggest is an effective treatment, and this intervention alone may be responsible for the improvement in glucose homeostasis in the first day of life.

The effects of amino acids on insulin secretion is well described in preterm infants, Denne et al. [11] demonstrated a significant increase in plasma insulin concentrations in extremely preterm infants in response to PN consisting of glucose, lipid and amino acids, but the increase in insulin concentration could have been secondary to infusion of any of the three substrates or a combination thereof. Thureen et al. [12] in randomized controlled trial in very preterm neonates of early parenteral administration of amino acid low (1g/kg/d) versus high (3g/kg/d), to test the safety and efficacy of early amino acid intake, demonstrated an approximate doubling of insulin concentrations in intake in the high amino acid group.

Using a euamoni academic clamp in neonatal piglet model, Wray-Cahen et al. [13] demonstrated that whole body amino acid disposal rate was related to the insulin concentration, and was more sensitive to insulin concentration in the younger (7d) than older (26 d) animals. Our results was similar with the report of [8] that increasing early protein intake is associated with a reduction in insulin-treated hyperglycemia in infants <29 weeks gestation. The use of insulin therapy allows the potential benefits of a high nutrient intake strategy may have direct benefits for growth and development; however concerns remain about the risk of hypoglycemia and neurologic potential risks.

Early protein may produce a sustained effect on glucose metabolism by altering insulin-like growth factor I (IGF-1) concentration. IGF-1 lowers blood glucose levels by increasing peripheral glucose uptake and glycogen synthesis as well as suppressing hepatic glucose production and is stimulated by insulin [14]. Evidence suggests that IGF-1 concentration is positively correlated with neonatal protein intake and nitrogen balance. Higher levels of IGF-1 are associated with improved growth following preterm birth in the catch-up phase of growth;

however there is a lack of evidence of the effect of protein intake and IGF-1 activity immediately after birth [8].

Previously have been described that early introduction of amino acids (without fat emulsion) increases hypoglycemia in the first 48 hours [15], however in this study the hypoglycemia may be related to the energy intake of the glucose/amino acid relation group not meeting the energy cost of increased protein synthesis following the administration of amino acids. In our study, for the variable hypoglycemia we found a low frequency of hypoglycemia in the group of early amino acids (1.4% vs. 15.5%).

Our special preterm solution was prepared with the possibility of be administrated by peripheral venous catheterization, with the intention to start the amino acid infusion in the first hour of life, however the rate of amino acids was 2.3g/kg/day. While high amino acids infusions commencing immediately after birth (>3g/kg/day) may mimic the observed high amino acids oxidation rate seen in utero, preterm newborns must function without the help of the placenta to remove potentially toxic metabolites [16].

A randomized controlled trial data showed that 3.6g/kg/day gave no additional advantage to 2.4g/kg/day in the first 48h with respect to nitrogen accretion, but was associated with more metabolic imbalances [17], while another showed improved head growth on ≈2g/kg/day during the first 2 days increasing to 3.8g by day 5 [18].

Conclusion

Our results demonstrate that EA initiation is associated with decreased hypoglycemia and hyperglycemia in extremely low birth weight infants. EA administration should be used as part of the strategy to reduce the risk of hyperglycemia thereby minimizing the need for insulin treatment. Optimizing the timing of amino acid therapy by initiation earlier treatment may carry additional benefits on protein accretion and nutrition regimens should be refined to ensure the minimum of interruption to nutrient provision.

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