Summary
Randomized Control Trial Evaluating the Effect of Two Different Doses of Amino Acids on Growth and Serum Amino-Acids in Premature Neonates Admitted to the NICU

Sponsor
Pediatrix Medical Group, Inc. and Pediatrix Screening Laboratories

Steering Committee
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Purpose
The purpose of this study is to measure the effect of two distinct strategies of parenteral nutrition supplementation on serum amino acid profiles and on growth to 28 days of life.

Study Type: Randomized Dose Comparison Concurrent Control Trial

Study Design
Randomization will be completed by computer generated randomization logs distributed to the research pharmacist at each site. Each site pharmacy will prepare the assigned parenteral nutritional supplementation.

**Group 1** - begin supplementation with 1.0 gram/kg/day of amino acids and advance by 0.5 grams/kg/day to a maximum of 2.5 grams/kg/day on day 4. Maximum allowable supplementation = 2.5 grams/kg/day.

**Group 2** – begin supplementation at 1.5 grams/kg/day of amino acids and advance by 1 gram/kg/day to a maximum of 3.5 grams/kg/day on day 3. Maximum allowable supplementation = 3.5 grams/kg/day.

Multicenter Study – 10 centers
Expected Enrollment: 120 – 150 subjects

Eligibility

Inclusion Criteria
Documentation of informed consent
Inborn
Gestational age between 23 weeks and 0/7 days and 29 weeks and 6/7 days (ability to follow subjects transferred to another facility for lab tests and outcome data)
No major anomalies
(chromosomal abnormalities, cyanotic congenital heart disease, gastrochisis, omphalocele, diaphragmatic hernia or other major gastrointestinal anomalies, major neurological injury or anomalie, and multiple congenital anomalies)
Ability to begin parenteral nutrition within the first 48 hours after birth

Exclusion Criteria
Outborn
Gestational age >= 30 weeks
Any major congenital anomalies

Primary Endpoint
Weight gain (weight growth velocity gram/kg/day) during the first 28 days after birth.

6.6.2005 Version 4
Secondary Endpoints
1. Head circumference and length measurements on day 28.
2. Serum amino acid profiles on day of randomization, day 7 and day 28 of life.
3. Occurrence of any of the following during the first 28 days after birth:
   necrotizing enterocolitis, blood culture proven sepsis and/or positive CSF culture or
   meningitis, IVH, and/or death.

Summary
Malnutrition is a common problem in the neonatal intensive care unit.(1) Recent studies
indicate that prematurely born neonates commonly develop a severe nutritional deficit during
the first weeks after birth, referred to as extrauterine growth restriction.(2) Despite an increase in
growth during the second month of hospitalization, many neonates are ultimately discharged
home having grown inadequately. The early nutritional deficit affects weight gain as well as
growth in length and head circumference.(3)

Growth measurements such as weight, length, and head circumference are macroscopic
measures of nutritional status and underestimate the physiologic consequences of prolonged
nutritional deprivation. Energy and micronutrient deficiencies alter growth at a cellular and tissue
level before macroscopic measures are altered. In the brain, for instance, energy is required for
cell division and neuronal growth, glial cell function, and myelination. Energy deprivation may
consequently alter neuronal function and growth, resulting in adverse neurodevelopmental
outcome.

A recent study suggests that postnatal malnutrition and growth restriction are inevitable if
current recommended dietary intakes are followed.(2) Multicenter studies show that variation in
dietary intake accounts for 45% of the variation in growth.(3) Hence, efforts have focused on
determining whether nutritional deficiency and the observed growth restriction of premature
infants can be prevented through the use of more optimal nutritional intake. In addition,
inadequate protein support may be a primary cause for growth failure.(4)

Based on animal studies showing high in utero amino acid flux observed during the latter
phase of gestation, Thureen et al have (5) have suggested the use of higher doses of amino-
acid supplementation in order to minimize growth restriction and improve outcome of premature
infants. However there are no large human trials that demonstrate that this approach promotes
better growth or that it is safe. While small doses of amino-acids may be inadequate to promote
normal growth, high doses may lead to elevated serum amino-acid levels and increase the
occurrence of toxicity. Through the implementation of a multicenter, randomized trial and
tandem mass spectrometry, we propose to evaluate the effects of two distinct strategies of
amino acid supplementation on serum amino acid profiles and growth of premature infants
during the first 28 days of life.

Reference List

(1) Clark RH, Wagner CL, Merritt RJ, Bloom BT, Neu J, Young TE et al. Nutrition in the neonatal intensive care unit: how do we
    reduce the incidence of extrauterine growth restriction? J Perinatol 2003; 23(4):337-3


(3) Bloom BT, Mulligan J, Arnold C, Ellis S, Moffitt S, Rivera A et al. Improving growth of very low birth weight infants in the first
    28 days. Pediatrics 2003; 112(1 Pt 1):8-14.

(4) Olsen IE, Richardson DK, Schmid CH, Ausman LM, Dwyer JT. Intersite differences in weight growth velocity of extremely

(5) Thureen PJ, Mela D, Fennessey PV, Hay WW, Jr. Effect of Low versus High Intravenous Amino Acid Intake on Very Low