SUMMARY

How Illness and Nutritional Support Influence Amino Acid and Acylcarnitine Profiles in Premature Neonates

Sponsor
Pediatrrix Medical Group, Inc.

Steering Committee
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Study Type
Prospective Descriptive Study

Multicenter Study – 20 sites
Enrollment Goal – 1000 participants

Study Population
Inclusion Criteria
1. Documentation of informed consent
2. Inborn
3. Less than or equal to 24 hours of age
4. Gestational age between 23 weeks and 0/7 days and 31 weeks and 0/7 days as per the best estimate by the neonatologist
5. If subject is transferred to another hospital, the ability to obtain follow-up data on outcomes
6. No major anomalies (inborn error of metabolism, chromosomal abnormalities, cyanotic congenital heart disease, gastrochisis, omphalocele, diaphragmatic hernia or other major gastrointestinal anomalies, major neurological injury or anomaly, and multiple congenital anomalies)

Exclusion Criteria
1. Outborn (transferred for intensive care from another hospital)
2. Greater than 24 hours of age
3. Gestational age < 23 weeks or > 31 weeks
4. Any major congenital anomalies

Purpose
The goals of this study are:
1. To better define normal amino acid and acylcarnitine values and how they change in premature neonates
2. To measure the effect nutritional support has (breastmilk vs. formula) on amino acid and acylcarnitine profiles
3. To measure the effect of illness (parenteral nutrition associated cholestatis) on amino acid and acylcarnitine profiles
4. To better define abnormal metabolic profiles (low tyrosine levels) in neonates that have hypothyroidism
Outcome Measures
Primary and Secondary Outcome Measures
1. Metabolic Profile - Serum amino acid, acylcarnitine and thyroxine levels
   • day of birth – day of enrollment, (birth date is day zero)
   • at 7 days (parenteral nutrition effect), and
   • at 28 days (established enteral nutrition effect)
   • at 42 days (established enteral feedings and growing)

2. Occurrence of any of the following
   • death
   • cholestatic liver disease (direct serum bilirubin above 5 mg/dl) and with no history to suggest viral hepatitis
   • blood culture proven sepsis and/or positive CSF culture or meningitis
     - less than 7 days – neonatal sepsis
     - after 7 days – nosocomial sepsis
   • necrotizing enterocolitis,
   • intraventricular hemorrhage (IVH),
   • need for respiratory support at 36 weeks post menstrual age

Summary of Problem
Malnutrition is a common problem in the neonatal intensive care unit. 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. 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.

Growth measurements such as weight, length, and head circumference, however, 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.

In our randomized control trial, the use of a higher dose (higher initial dose, faster advancement, and higher maximum dose) of amino acids in parenteral nutrition did not promote improved growth (weight gain or changes in length and head circumference) compared to a lower dose of amino acid supplementation. In addition, several blood amino acids acylcarnitine values were higher by day 7 in patients treated with the higher dose approach. In both treatment groups, some amino acid acylcarnitine values were commonly above the 90th percentile while other amino acid acylcarnitine values were commonly below the 10th percentile compared to a normal term newborn reference. Although none of the values reached the threshold for diagnosis of serious “metabolic” disease, we cannot be certain that these levels are “safe” in the preterm infant.

Similar to te Braake et al. and Poindexter et al., our study demonstrates that the dose of parenteral amino acid supplementation increases blood amino-acid levels, especially during the parenteral phase of nutrition. The increase in amino acids seen on day 7 suggests that some amino acids accumulate in the blood, presumably because protein
anabolism may be saturated, or the anabolic pathway is immature and the premature neonate cannot process the extra amino acids. Leucine and isoleucine are major amino acid components of both TrophAmine and Aminosyn. The elevated levels of leucine-isoleucine [Figure 1] and isovaleryl carnitine (a product of L-leucine metabolism) provide evidence that giving higher doses of leucine to premature infants would be futile (pathway saturation). Furthermore, the elevated concentrations of isovaleryl carnitine suggest that the blood isovaleric acid levels may begin to approach levels that are associated with toxicity in some premature infants, as seen in Isovaleric Acidemia. L-carnitine administration in the parenteral nutrition mixture might explain why some acylcarnitine levels were high but it does not explain the day 7 differences between the two treatment groups in isovaleryl carnitine levels [Figure 2] In contrast, some amino acid (alanine, glutamate, phenylalanine, tyrosine) levels were low compared to normal newborns and supplementation also influenced the incidence of low values. [Figures 3 and 4]

Our data suggest that current strategies of nutritional support result in excess levels of some amino acids and acylcarnitine values and inadequate concentrations of other amino acids and acylcarnitine values. As in our previous work we will use tandem mass spectroscopy to measure several key amino acid and acylcarnitine values to evaluate the metabolic status of the patient. This profile of values is identified below and we will call this a metabolic profile. There is an important limitation to this observation – there is no standard reference. Each state has its own set of procedures for identifying neonates with inborn errors of metabolism and there are no nationally accepted standards that are universally applied.5-8 Establishing a consensus on what represents a normal amino acid profile in premature neonates would allow investigators to identify neonates with “abnormal” values and evaluate the impact of these abnormal values on important health outcomes (infection, necrotizing enterocolitis, growth, and neurodevelopmental outcome). Understanding how different forms of nutritional support influences amino acid and acylcarnitine is also essential to defining normal and establishing normal values will facilitate our ability to monitor the adequacy of amino acid acylcarnitine supplementation.

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<thead>
<tr>
<th>Amino Acids</th>
<th>Acylcarnitines</th>
<th>Thyroid</th>
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<tbody>
<tr>
<td>Alanine</td>
<td>Acetyl (C2)</td>
<td>Thyroxine</td>
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<tr>
<td>Arginine</td>
<td>Butyryl (C4)</td>
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<tr>
<td>Aspartate</td>
<td>Free Carnitine</td>
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<tr>
<td>Citrulline (119)</td>
<td>Glutaryl (C5DC)</td>
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<tr>
<td>Glutamate</td>
<td>Isovaleryl (C5)</td>
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<tr>
<td>Glycine</td>
<td>3-hydroxyisovaleryl (C5OH)</td>
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<tr>
<td>Histidine</td>
<td>Linoleyl (C18:2)</td>
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<tr>
<td>Leucine-Isoleucine</td>
<td>Oleyl (C19:1)</td>
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<tr>
<td>Methionine</td>
<td>Palmitoyl (C16)</td>
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<tr>
<td>Ornithine</td>
<td>Palmitoleoyl (C16:1[N-7]</td>
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<tr>
<td>Phenylalanine</td>
<td>Propionyl (C3)</td>
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<td>Tyrosine</td>
<td>Succinyl (C4DC)</td>
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<tr>
<td>Valine</td>
<td>Free Carnitine (FC)</td>
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References


