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Randomized Controlled Trial

Enhanced nutrient supply to very low birth weight infants is associated with higher blood amino acid concentrations and improved growth

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SUMMARY

Background & aims: Customized nutrient supply is vital to ensure optimal growth among very low birth weight infants (birth weight < 1500 g). The supply of amino acids is especially important due to their impact on protein synthesis and growth. The objectives of this study were to evaluate the impact of enhanced nutrition on growth, blood concentrations of amino acids, and explore possible associations between amino acid concentrations and common neonatal morbidities. We hypothesized higher amino acids levels and growth velocity among infants on enhanced nutrient supply.

Methods: This randomized controlled trial was performed in three university neonatal intensive care units in Oslo, Norway. Fifty very low birth weight infants were randomized to a control or intervention group. Within 24 h after birth, infants in the intervention group received enhanced supply of energy, amino acids, lipids, long-chain polyunsaturated fatty acids and vitamin A, whereas the control group received a standard nutrient supply. The intervention continued until 52 weeks postmenstrual age or until a body weight of 5.5 kg was reached. Amino acid analyses were performed at birth, day 3, 5 weeks of age and 5 months corrected age. Detailed information about nutrient intake, morbidities, blood amino acid concentrations and growth velocity were collected from 44 infants (6 infants excluded). High-performance liquid chromatography was used for amino acid analysis.

Results: The intervention group ($n = 23$) received higher supply of proteins, with higher blood concentrations of amino acids measured at 5 weeks of age, and improved growth velocity (mean 17.4 vs 14.3 g/kg/day, $p < 0.001$) at 36 weeks postmenstrual age, compared to the control group ($n = 21$). The correlation between concentrations of branched chain amino acids (leucine, isoleucine and valine) and growth was stronger and more positive among infants: a) in the control group (correlation coefficient ≥ 0.68, $p \leq 0.004$); b) born with birth weight appropriate for gestational age (correlation coefficient ≥ 0.53, $p \leq 0.009$) and c) not diagnosed with septicemia (correlation coefficient ≥ 0.63, $p \leq 0.005$).

Conclusion: Enhanced nutrient supply to very low birth weight infants led to higher blood amino acid concentrations and improved growth. The correlations between amino acid concentrations and growth

Abbreviations: AA, Amino Acid; BPD, BronchoPulmonary Dysplasia; BW, Birth Weight; GV, Growth Velocity; PMA, Post Menstrual Age; SGA, Small for Gestational Age; VLBW, Very Low Birth Weight.

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velocity were weaker in the intervention group as compared to the control group. This could reflect an upper threshold for protein synthesis and growth with our intervention, whereas a potential for further growth with increasing amino acid supply was possible for the control group.
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1. Introduction

Preterm birth is a leading cause of neonatal morbidity and mortality [1]. Despite medical advances, impaired cognitive function, postnatal infections, lung disorders, and growth restriction are common co-morbidities among preterm born infants [2,3]. The purpose of supplying customized nutrition to premature infants is to achieve growth similar to normal fetal growth [4]. However, the nutritional requirements are seldom met with subsequent postnatal growth restriction as a result [5]. We previously demonstrated an increase in the proportion of growth-restricted very low birth weight (VLBW, birth weight (BW) < 1500 g) infants from birth (33%) to discharge (58%) [6]. Enhanced nutrient supply is associated with improved cognitive development and brain maturation [7–9], where proteins have a central role [10]. Proteins are made up of amino acids (AAs) where some AAs are classified as essential and must be provided in order to prevent disease. Others are non-essential and conditionally essential, the latter with limited synthesis during certain conditions like prematurity. Depletion of certain AAs have been associated with common neonatal morbidities such as increased risk of infections and lung disorders with low levels of arginine [11,12]. In addition, the branched-chain AA leucine may have anabolic properties and enhance muscle protein synthesis and growth during the neonatal period, although there is limited knowledge and further investigation is recommended [13].

To evaluate the effect of an enhanced nutrient supply we performed a randomized controlled trial where infants in the intervention group received increased supply of energy, AAs, lipids, vitamin A and essential long-chain polyunsaturated fatty acids. After enrollment of 50 infants, a pre-planned safety analysis revealed an increased occurrence of late onset septicemia in the intervention group [14]. Thus, further inclusion of infants was stopped. We suggested that early AA intake, followed by increased insulin production and transfer of phosphate into cells for energy and protein production might have induced low plasma concentrations of phosphate and potassium and promoted phagocyte dysfunction with septicemia as a result [14]. The intervention group achieved postnatal growth along their birth percentiles for weight and head circumference, whereas the control infants fell below their growth trajectories [15]. Magnetic resonance diffusion tensor imaging, performed close to term-equivalent age, demonstrated improved cerebral maturation [8], and visual event-related potentials (non-invasive recording of cortical neural responses) performed at 5 months corrected age, showed a more consistent response to global motion among infants on enhanced nutrient supply, as compared to the control group [9].

The objectives of this follow-up study were to evaluate the impact of enhanced nutrition on blood concentrations of AAs, especially the branched-chain AAs, and explore possible associations between AA concentrations, growth and common neonatal morbidities associated with premature birth. We here hypothesized enhanced AA levels and improved growth among infants in the intervention group, without increase in neonatal morbidities.

2. Materials and methods

2.1. Study design

This open and randomized controlled multi-intervention, nutritional study was performed in three neonatal intensive care units in Oslo, Norway (Akershus University Hospital and Oslo University Hospital: Ullevål and Rikshospitalet) in 2010. The primary objective was to reduce the proportion of VLBW infants discharged from hospitals as growth restricted. Secondary objectives were to achieve growth velocity (GV) similar to normal intrauterine growth rates, evaluate blood AAs concentrations and optimize cerebral development. The study was approved by the Regional Committee for Medical and Health Research Ethics and performed in accordance with the Helsinki Declaration. All VLBW infants born at the participating units were eligible for inclusion and randomized as previously described [15].

2.2. Nutritional intervention

The nutritional intervention was initiated within 24 h after birth. Infants in the intervention group received enhanced supply of energy, AAs, lipids, long-chain polyunsaturated fatty acids and vitamin A, whereas the control group received nutrient supply according to standard recommendations. The intervention group started with 3.5 g/kg/day of AAs, whereas the control group received 2.0 g/kg/day. The protein supply was gradually increased in both groups, mostly by enhancing the enteral supply of unfortified and fortified human milk. All infants received human milk. The protocol was identical in all participating units. A detailed description of the nutrient intervention has been published elsewhere [15]. The calculated difference was 10% for energy and 20% for protein, estimated to cover the cumulative deficits generated during the fetal and early postnatal period. During the first 4 weeks the intervention group received a median of 139 kcal/kg/day of energy and 4.0 g/kg/day of AAs, whereas the control group received 124 kcal/kg/day of energy and 3.2 g/kg/day of AAs. The supply of carbohydrates was kept similar in both groups, with a minimum supply of 5.8 g/kg/day on day 1. The nutritional intervention was adjusted according to protocol and continued until 52 weeks postmenstrual age (PMA) or until the infant weighed 5.5 kg.

2.3. Amino acid supply

All infants received AAs enterally and parenterally. The enteral supply was from fortified human milk. Both groups received human milk fortified with Nutriprem (Nutricia, Norway) whereas the intervention group received additional AA fortification with Complete Amino Acid Mix (Nutricia). Human milk [16], Nutriprem and Complete Amino Acid Mix contain the following essential AAs: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine; the non-essential AAs: alanine, aspartic acid, glutamic acid and serine, and the conditionally essential AAs: arginine, glycine, proline, tyrosine and cysteine. Human milk and Complete Amino Acid mix contain the non-

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