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Early and intensive nutritional strategy combining parenteral and enteral feeding promotes neurodevelopment and growth at 18 months of corrected age and 3 years of age in extremely low birth weight infants

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ABSTRACT

Aim: To evaluate whether aggressive nutrition can improve long-term neurodevelopmental outcomes and growth in extremely low birth weight (ELBW) infants born appropriate for gestational age (AGA).
Methods: This single-center cohort study included 137 ELBW AGA infants born in two epochs. The first group received standard nutrition (SN; $n = 79$) consisting of amino acids started at 0.5 g/kg/day on Day 4 of life and increased to 1.0 g/kg/day. The second aggressive nutrition (AN) group received amino acids started at 1.5–2.0 g/kg/day within 24 h of life and increased to 3.5 g/kg/day. Parenteral and enteral feedings were combined in both groups. Neurodevelopmental outcomes by the Kyoto Scale of Psychological Development and growth were followed up to 18 months of corrected age or 3 years of age and compared by univariate and multivariate analyses.
Results: Baseline characteristics were similar between the two groups. At 3 years of age, AN children had a significantly greater mean value of head circumference, but not length or weight, than SN children (49.1 vs 48.0 cm, $p = 0.014$). The cognitive-adaptive (C-A) score in the AN group was also significantly higher than that in the SN group (98.3 vs 91.9 at 18 months, $p = 0.039$ and 89.5 vs 83.1 at 3 years, $p = 0.047$). AN infants born ≥26 weeks of gestation were less likely to develop borderline disability in C-A, language-social and overall developmental scores compared to gestational age-matched SN infants.
Conclusion: Parenteral and enteral AN after birth improved the long-term cognitive neurodevelopment in ELBW AGA infants, especially in those born ≥26 weeks of gestational age, however results need to be confirmed in a larger, multi-site randomized trial.

1. Introduction

Extremely low birth weight (ELBW) infants often accumulate significant nutrient deficiencies in the first few weeks of life, particularly in the first week. The principles of such organizations as American Academy of Pediatrics (AAP) [1], the Canadian Paediatric Society (CPS) [2], and the European Society of Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) [3,4], are similar, namely to provide nutrients to approximate the rate of growth and composition of weight gain for a normal fetus of the same postmenstrual age, to maintain normal concentrations of blood and tissue nutrients and to achieve a satisfactory functional development [5]. However, unfortunately the composition of the optimal nutrients for the proper intrauterine growth rate is unknown, the current recommended dietary intake may be still not sufficient to replace these deficits [6] and extrauterine growth restriction (EUGR) remains common in ELBW infants [7]. A number of clinical investigations of postnatal inpatient nutrition and growth and subsequent outpatient growth and development show the following [5]: better nutrition is associated with improved growth and less EUGR [8–16], improved growth is associated with improved neurodevelopmental outcomes [14–19,20–22], and better nutrition is associated with improved neurodevelopmental outcomes [15,16,23,24].

Antenatal and postnatal growth, especially in head circumference, is associated with long-term neurodevelopmental outcomes [16,25].

Abbreviations: AA, amino acid; AGA, appropriate for gestational age; AN, aggressive nutrition; BPD, bronchopulmonary dysplasia; CA, corrected age; C-A, cognitive-adaptive; CI, confidence interval; DA, developmental age; DQ, developmental quotient; ELBW, extremely low birth weight; FEF, full enteral feeding; KSPD, Kyoto Scale of Psychological Development; L-S, language-social; MDI, Mental Developmental Index; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; OR, odds ratio; PDA, patent ductus arteriosus; P-M, postural-motor; PMA, postmenstrual age; ROP, retinopathy of prematurity; SN, standard nutrition.

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To minimize the early postnatal nutrients deficit, therefore, parenteral and enteral high amino acid (AA) intakes initiated early after birth have rapidly become a part of the routine care of prematurely born infants. A number of studies have reported the safety and beneficial short-term effects [10,11]. On the other hand, a Cochrane systematic review has suggested that early administration of AAs promotes a positive nitrogen balance but the effect of early AA administration on long-term neurodevelopmental outcomes has not been reported, and clinical and statistical heterogeneity of the studies is insufficient evidence from randomized controlled trials [26]. However, the nutritional protocol of several studies included was not identical, and few studies have been conducted on the long-term prognosis of premature infants receiving early aggressive nutritional therapy.

Therefore, it remains unknown whether high protein supplementation in ELBW infants improves long-term neurodevelopmental outcomes. The aim of the present study was to evaluate the effect of early aggressive nutrition by both parenteral and enteral routes in ELBW infants on long-term neurodevelopmental outcomes and growth up to 18 months of corrected age (CA) and 3 years of life.

2. Methods

2.1. Data collection

This cohort study was performed in a single tertiary center in Japan. Informed consent was obtained from all parents at birth, and the study was approved by the institutional medical ethics committee. ELBW infants admitted to the Neonatal Intensive Care Unit (NICU) at the Osaka City General Hospital were recruited prospectively between April 2004 and December 2010 and prescribed aggressive nutrition (AN). Their data were compared to retrospectively collected data of ELBW infants who were admitted to the NICU between January 1994 and December 1999 and received standard nutrition (SN). The data were collected from the medical records and database of the hospital. The initial enrollment criteria were birth weight of <1000 g and appropriate-for-gestational age (AGA). Infants who were small for gestational age (SN 25.2% vs AN 34.3%) or large for gestational age (12.2% vs 10.1%) or with death (18.7% vs 12.6%), intraventricular hemorrhage (papile 1–4 degree, 14.5% vs 12.6%), periventricular leukomalacia (1.2% vs 2.3%), gastrointestinal perforation (5.8% vs 4.4%), and congenital anomalies or diagnosed syndrome (8.2% vs 11.1%) were excluded to affect nutrient metabolism and neurodevelopment. There were 137 AGA ELBW infants that satisfied these criteria (79 SN and 58 AN). Of those, 124 (73 SN and 51 AN) had follow-up records up to 18 months of CA, and 119 (71 SN and 48 AN) up to 3 years of age.

The following demographic data were obtained for all preterm infants born during the study period: gestational age; birth weight; head circumference at birth; sex; mode of delivery, singleton or multiple pregnancy; and 1- and 5-minute Apgar scores. Morbidity parameters included: days requiring assisted ventilation; need for oxygen support at 36 weeks of PMA; preventive or therapeutic use of indomethacin for patent ductus arteriosus (PDA), ligation of symptomatic PDA; and retinopathy of prematurity (ROP) requiring photocoagulation. Nutritional data obtained were cumulative amounts of carbohydrate, protein and calorie intakes by parenteral and enteral routes for the first 28 days after birth. Full enteral feeding (FEF) was established at 100 ml/kg/day. Days to regain birth weight and days to FEF were also analyzed. In addition, neonatal growth parameters (weight, head circumference and length) at 12 months of age and 3 years of age and neurodevelopmental quotient scores at 18 months of CA and 3 years of age were obtained.

2.2. Nutritional protocols

All infants in the NICU from January 1994 to December 1999 received SN. Fluid intake was started at 60 ml/kg/day on the first day of life (Day 1) and increased by 10 to 20 ml/kg/day until about 150 ml/kg/day was achieved. AA solution (Preamin-P, Fuso Pharmaceutical, Osaka, Japan) was started at 0.5 g/kg/day on Day 4, increased in increments of 0.5 g/kg every 24 h to a maximum of 1.0 g/kg/day and continued until FEF was achieved. Lipids supplementation (Intralipid, Terumo Pharmaceutical, Tokyo, Japan) was started at 0.5 g/kg/day on Day 7 and advanced by 0.5 g/kg/day to a maximum of 1.0 g/kg/day. Parenteral AA and lipids were decreased accordingly with increased enteral nutrition and discontinued at attainment of FEF. Along with enteral nutrition, breast milk or a term formula was also started at 2 to 5 ml/kg/day between Days 4 and 7. When FNF was established, half of the total enteral nutrition intake was replaced by fortified breast milk or a preterm formula, and medium-chain triglyceride oil was started at 2 to 3 ml/kg/day.

Infants born between April 2004 and December 2010 received AN. AA solution was started at 1.5 to 2.0 g/kg/day parenterally within 24 h of life and increased in increments of 1 g/kg every 24 h to a maximum of 3.5 g/kg/day. Parenteral AA was decreased accordingly on advancing enteral nutrition and discontinued when FEF and approximately 150 ml/kg/day of total fluid intake were achieved. Lipids supplementation was started at 0.5 g/kg/day on Day 3 or 4 and increased by 0.5 g/kg/day to a maximum of 2.0 g/kg/day. Breast milk or a term formula was started at 5 to 10 ml/kg/day on Day 1 and advanced more rapidly than SN. When FEF was achieved, all of the enteral nutrition intake was replaced by fortified breast milk or a preterm formula, and medium-chain triglyceride oil was started at 2 to 3 ml/kg/day.

Glucose, minerals, trace elements and vitamins were prescribed for all infants according to the institutional protocol and as tolerated by each infant. Trophic feeding was introduced as soon as the infant was metabolically stable and had evidence of gastrointestinal motility. Initiation and advancement of oral feeding were determined by the neonatologist. Laboratory hematology values were evaluated every day during parenteral nutrition to examine adverse effects. The AA supplementation was discontinued when serum blood urea nitrogen was >60 mg/dl and plasma ammonia was >150 mg/dl.

2.3. Follow-up

All surviving infants were enrolled in a premature infant developmental evaluation program that consisted of hospital visits immediately after discharge and at 4, 7, 12, 18 and 24 months of corrected age and 3 years of age. Actual mean age of follow-up consultation for the 12, 18 months of corrected age, and 3 years of age is AN vs SN, 12.1 vs 12.3 at 12-month, 18.3 vs 18.4 at 18-month, and 36.3 vs 36.5 at 3-year (36-month). At each visit, medical history taking and growth evaluation were performed. Physical and neurological examinations were performed by an experienced neonatologist in the follow-up program.

2.4. Anthropometric measurements

Trained nurses measured at the follow-up examination until 3 years of age. Body weight was measured using digital electronic scales reading to the nearest gram. Recumbent body length was measured using a length board in 12 months, after the children were measured standing. One examiner held the infant's head in a vertical position with the top of the head touching the fixed headboard, while second examiner extended the legs and firmly placed the movable footboard against the heels. Because recumbent body length is measured using a length board in 12 months, but a standing position and the recumbent position for the measurement are mixed in 18 months, we adopted 12 months. Occipitofrontal head circumference was measured by placing a paper measurement tape firmly around the head at the most prominent part of the frontal bulge and the part of the occiput that gave the maximum circumference.