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Original article

Early parenteral lipids and growth velocity in extremely-low-birth-weight infants☆

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SUMMARY

Background & aims: Whether early parenteral lipids improve postnatal growth of preterm neonates remains unclear. We aimed to assess the effects of parenteral lipids on growth velocity in extremely-low-birth-weight infants.

Methods: This retrospective cohort study included 121 extremely-low-birth-weight infants. The associations between parenteral lipids (cumulative intakes during the first week and delays in their introduction) and growth velocities (weight, head circumference and length) up to 28 days of life and to 36 weeks of corrected age were analysed using uni- and multivariate linear regression.

Results: Univariate analyses showed a significant positive association between the cumulative intakes of parenteral lipids during the first week and i) weight gain up to day 28; ii) weight gain up to 36 weeks of corrected age; iii) head circumference growth up to day 28. There was a negative correlation between the delay in parenteral lipid introduction and weight gain up to day 28. In multivariate analyses, the association between the cumulative intakes of parenteral lipids and weight gain up to 28 days was independent of gestational age at birth, birth weight, sex, smallness for gestational age, and enteral intakes (regression coefficient: 0.19; 95% CI: 0.01–0.38) and, up to 36 weeks, independent of gestational age, birth weight, sex, smallness for gestational age and parenteral glucose and amino acids (0.16; 95% CI: 0.04–0.27).

Conclusions: Parenteral lipids during the first week were positively associated with weight gain in extremely-low-birth-weight infants and could improve early nutritional support of preterm neonates.

1. Introduction

The importance of nutritional support for preterm neonates is becoming increasingly established.[1,2] A major goal in the initial management of these infants is to allow them to grow at similar rates than *in utero* (>15 g/kg/day).[3] However, despite the accumulated evidences and recommendations advocating more "aggressive" nutrition, post-natal growth restriction remains a common complication, especially in the extremely-low–birth-weight (ELBW) infants.[4] Postnatal growth failure is associated with short- and long-term negative impact on health and neuro-development.[5,6] There is therefore a real need to further develop strategies improving postnatal growth in these high-risk neonates.[7]

The first week of life offers a critical window to limit postnatal nutritional and energy deficits.[8] Aggressive early intakes of

Abbreviations: BW, birth weight; CA, corrected age; 95% CI, 95 percent confidence interval; DoL, day of life; EFA, essential fatty acids; ELBW, extremely low birth weight; GA, gestational age; HC, head circumference; IVH, intra-ventricular haemorrhage; MCT, medium-chain-triglycerides; NICU, neonatal intensive care unit; PUFA, polyunsaturated fatty acids; SD, standard deviation; SGA, small for gestational age.

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parenteral amino-acids and energy have been associated to improved growth and neurodevelopment.[9,10] Lipids provide energy and essential fatty acids (EFA), both important for growth and neurodevelopment. EFA are precursors for the synthesis of long chain polyunsaturated fatty acids which play a structural role in biological membranes and are notably involved in retinal and cerebral development.[11] Due to their rapid brain growth and low endogenous stocks, preterm neonates are particularly vulnerable to EFA deficiency.[12,13] Furthermore lipids provide high-density energy important in reducing early energetic deficit and in enhancing protein accretion, growth and neurodevelopment. Despite these theoretical interests, clinical benefits of early parenteral lipids remain unclear. Due to concerns about potential side effects, most studies focused on their security or on their tolerance, while data on growth or development remain limited and inconclusive.[14–16] Two systematic reviews showed no significant differences between aggressive or less aggressive lipid regimens in terms of mortality, morbidity and growth.[17,18] Their authors however underlined that data on growth velocities were insufficiently reported.

Therefore, there are no precise recommendations regarding timing of introduction or doses of parenteral lipids during the first days of life.[19] Significant variations are reported in practices, not only between different centres, but also within a single centre.[20,21] A preliminary study showed that significant delays in parenteral lipid introduction exist and that intakes during the first days are often inferior to current recommendations.[22]

We performed a cohort study to determine whether parenteral lipid intakes during the first week of life were associated to growth velocity in ELBW infants, up to 28 days of life and to 36 weeks of corrected age (CA). We also studied the effect of the delay in parenteral lipid introduction on growth velocities.

2. Material and methods

2.1. Study design, participants, and setting

This retrospective cohort study was conducted in a 52-bed tertiary level Neonatal Intensive Care Unit (NICU). All preterm neonates weighing less than 1000 g at birth and admitted from January 2010 to December 2011 on their first day of life (DoL) were eligible. Newborns who died or were transferred to another NICU before day 28, newborns with incomplete nutritional or growth data, and newborns with major congenital malformations were excluded. In addition, those who developed post-hemorrhagic hydrocephalus were excluded from the analysis of head circumference (HC) growth. The study protocol was approved by the local Ethical Committee and exempted from informed consent.

2.2. Nutritional policies in the NICU

During the study period, all ELBW infants admitted to the NICU received nutritional support according to a single protocol based on the ESPGHAN recommendations.[19] Our protocol policy for initiation, progression, and targets of parenteral intakes is presented in Table 1.

Parenteral glucose and amino acids (Primene® 10%, Clintec Parenteral, Maurepas, France) were provided soon after birth. The introduction of parenteral lipids occurred after a recommended minimal delay of 24 h of life. Our protocol recommended reducing parenteral lipids in case of: i) same day surgery; ii) severe inflammatory state marked by a CRP $>$ 100 mg/L. The lipid emulsion used in the study was a physical mixture composed of 50% soybean oil and 50% coconut oil Medium-Chain-Triglycerides (MCT) (Medialipides® 20%, Braun Medical, Boulogne, France). Compared to pure soybean emulsion, it contains half of the Polyunsaturated Fatty Acids (PUFA).[12,19] Parenteral solutions, prescribed daily by the physicians, were prepared by the central pharmacy of the hospital except during the public holidays when the central pharmacy was closed. In the meanwhile, patients were given a mixture of amino acids, glucose and electrolytes prepared in the NICU.

Table 1
Parenteral nutritional protocol of the NICU during the study period.

Protocol	Parenteral lipids	Parenteral glucose	Parenteral amino acids
Time of introduction	>24 h of life	At birth	At birth
Initiation rate (g/kg/d)	1	6–8	2
Daily increase (g/kg/d)	0.5–1	1–2	0.5
Target (g/kg/d)	3–3.5	14–17	3.5

In parenterally fed infants, haemoglobin, haematocrit, platelet count, serum electrolytes, calcium, phosphorus, albumin and urea were checked at least weekly, and regimens were adapted by the attending physician. Triacylglycerolemia was not routinely performed during the study period. Glycaemia was monitored every 8 h on the first day, and then on a daily basis when normal. Insulin treatment was introduced when a glycaemia $\geq$ 11 mmol/L was confirmed on two laboratory tests. A reduction in glucose infusion was considered in case of refractory hyperglycaemia despite insulin introduction.

Human milk (mother's or donor's milk) was introduced on the first DoL and given daily at increasing doses from 5 to 10 mL/kg/d according to enteral tolerance assessed by gastric residuals (aspects and volumes) and abdominal distension. Once a minimum of 100 mL/kg/d was tolerated, human milk was supplemented with Eoprotine® (Milupa, Rueil Malmaison, France) and Liquigen® (Nutricia, Rueil Malmaison, France). In the case of confirmed intolerance it was advocated to maintain the same ratios of milk on the next day. The discontinuation of the enteral feeding was considered in the case of suspected necrotising enterocolitis or in highly unstable infants. The recommended total volumes of parenteral and enteral fluid intakes were 80 mL/kg/d on the first day, and were increased by 10 mL/kg/d to achieve 160 mL/kg/d.

2.3. Data collection and management

Clinical, nutritional and growth data were extracted from the infant's electronic medical charts. The clinical data included baseline characteristics and main morbidities during NICU stay. Nutritional data referred to the intakes of parenteral and enteral nutrients during the first week of life. The exact times of introduction of parenteral and enteral nutriments and the exact quantities delivered were systematically recorded in the electronic charts; this allowed calculating the real cumulative intakes of each nutriment during the first week. The parenteral nutrition prescriptions were checked against the pharmacy charts. The nutrient contents used for the calculations of the enteral intakes were: 1.1 g proteins, 6.6 g carbohydrates, and 3.9 lipids per 100 mL of human milk.

During the NICU stay, weight was measured daily on an electronic scale (accuracy $\pm$ 5 g) and crown-heel length and HC were measured weekly with a height gauge and a tape measure, respectively. Small for gestational age (SGA) status was defined as a birth weight (BW) two standard deviations (SD) below the mean on Usher and McLean growth charts.[23] The weight gain (in g/kg per day) was determined according to the formula: 1000 * [(weight on day 28 or week 36 − BW)/((weight on day 28 or week 36 + BW)/