Does early higher intravenous lipid intake decrease weight loss in very low birth weight infants? (REB-17-2236)

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Background:

The recommendation of the Pediatric Societies of North America and Europe is that postnatal growth of preterm infants matches the in-utero growth rates of fetuses that remain in utero until full-term.[1-3] Despite this long standing recommendation, approximately 43% to 97% of very low birth weight (VLBW, less than 1500 g) infants grow slower than the estimated fetal growth velocity.[4,5] This slow postnatal growth usually results in extra-uterine growth restriction (EUGR), defined as having a measured growth parameter (weight, length, or head circumference) that is less than 10th percentile of intrauterine growth expectation based on estimated postmenstrual age (PMA) in premature neonates at the time of hospital discharge.[4] EUGR is associated with major morbidities such as bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP) and impaired neurodevelopment.[4,6-8]

Although the etiology of EUGR is multifactorial, inadequate nutrition plays a pivotal role.[5,9] There are three critical stages of nutrition support in VLBW infants: (1) acute stage during the first 1-3 weeks after birth when infants are on parenteral nutrition, (2) intermediate period when infants are slowly advanced to full enteral nutrition (growing care stage), and (3) the post-discharge stage.[10] Failure to provide adequate nutrition in the acute stage result in cumulative energy and protein deficits that is difficult to reverse in the second stage. Inadequate early postnatal nutrition results in excessive weight loss that cannot be explained by the physiologic contraction of body water alone. The regain of birth weight may need two to three weeks or even longer in preterm infants with excessive postnatal weight loss.[11]

Newborn infants born at term normally lose 5-10% of their body weight in the first week of life due to contraction of extracellular water compartment.[12,13] The proportion of weight loss is significantly higher in VLBW infants.[12] Increased insensible water loss is widely considered as the main cause for additional weight loss in this population.[14,15] Nevertheless, studies identified low energy intake to be a key driver to excessive weight loss.[13,16] In fact, an earlier study showed that significant postnatal weight loss occurs mainly in infants whose energy intake is inadequate.[13] A more recent epidemiologic study demonstrated similar postnatal growth trajectories with minimal crossing of percentiles after the initial weight loss regardless of gestational age at birth.[11] The growth trajectories for infants in that study had similar slopes and growth rates which indicate that proportion of postnatal weight loss is a lead cause for EUGR at discharge.[11] Therefore, we speculate that decreasing the maximum percentage of initial weight loss in the acute stage would keep the preterm infant on a higher growth trajectory that is enough to reduce incidence of EUGR.

Current fat provision regimen for preterm infants include starting parenteral lipid at 12-24 hours of age with 0.5-1 g/kg per day and advancing by 0.5 g/kg/day until reaching 3 g/kg per day. Using early (within one hour of birth) and higher (start at 2 g/kg per day and advance to 3g/kg per day once total fluid intake is increased to 80 ml/kg/day) parenteral fat intake could reduce the cumulative caloric deficit in the acute stage. Because of high-density energy in fat, higher parenteral fat intake will reduce the early energy deficit and enhance protein accretion. The first 2-3 weeks of life offer a critical window to limit postnatal nutritional and energy deficits.[5] Recent study showed that higher energy and fat intakes during the first 2 weeks after birth are associated with a lower incidence of brain lesions and dysmaturation at term equivalent age in preterm neonates.[17]

To date, studies of "early aggressive nutrition" in preterm infants have mainly focused on high protein intake to prevent protein catabolism.[18-21] Nevertheless, provision of high protein intake without enough energy is unlikely to significantly reduce the early loss of protein and fat mass that had been accreted before birth. Early and high protein intake is currently a standard of care in our neonatal intensive care unit (NICU).

In summary, provision of high and early fat intake may help reducing the amount of postnatal weight loss. It may also help utilize the high amount of protein that is currently recommended to these premature babies. Also, we expect babies who get this appropriate intake to regain their birth weight earlier than others on slow fat increase regimen.

Methodology

Hypothesis:

We hypothesize that early higher fat intake in the first week after birth in VLBW infants results in less weight loss compared to the traditional provision of intravenous fat.

Study Design:

This is a randomized, non-blinded, controlled trial that will take place from March 2018 through February 2020 at the 39-bed level III NICU at Foothills Medical Center, Calgary, Alberta.

Intervention:

Starting Intravenous Lipid emulsions from D0 at 2 g/kg/day in the experimental group and increase to 3 g/kg/day the next day.

Comparison:

Control group: traditional start by 0.5-1 g/kg/day on D0 and increase daily by 0.5 g/kg/day till reaching 3 g/kg/day.

Outcome:

- Primary: The maximum percentage of weight loss in the acute stage of nutritional support: Defined as (birth weight−lowest postnatal weight)/birth weight× 100).

- Secondary:
    - Time to regain birth weight (day).
    - Time to reach 90 Kcal/kg/day (day).
    - Lipid tolerance: using serum TG levels (intolerance will be defined as TG> 2.8 mmol/L).
    - Incidence of EUGR at 36 weeks and at discharge.
    - Growth anthropometrics (weight, length and HC Z scores at 36 weeks and at discharge).
    - Incidence of ROP, BPD (28 days, 36 weeks CGA), brain injury and NEC.
    - Survival free major morbidity (BPD, ROP, NEC and severe IVH) at discharge.
    - Incidence of severe neurodevelopmental outcome at 18-22 months corrected gestation.
    - Length of stay.
    - Death.

Study Population:

a) Inclusion Criteria:

1. Preterm infants born with birth weight < 1500 g at Foothills Medical Centre (FMC)
2. Appropriate for gestational age (AGA) as per Fenton's growth charts
3. Anticipated duration of PN for >7 days

b) Exclusion Criteria:

1. Infants with congenital anomalies
2. Infants with suspected inborn errors of metabolism or family history of inborn error of metabolism
3. Infants with suspected or confirmed biliary atresia
4. Infants born small for gestational age (SGA)
5. Confirmed early sepsis

Twins and triplets who meet the weight and AGA status criteria will be randomized to the same arm of the study. Informed written consent will be obtained from a parent of each infant before birth or shortly after the infant's admission to the NICU and before starting parenteral lipid emulsions.

Time frame: March, 2018 to April, 2020

Study Protocol:

The investigators will conduct the randomization using a computer-generated allocation sequence (in random sized blocks for allocation concealment and balanced groups) generated at the University of Calgary. The lipid emulsions will be administered through an umbilical venous catheter, peripherally inserted central catheter, or peripheral line. The control group will begin treatment with 0.5 g/kg per day of 20% Intravenous Lipid Emulsion (IVLE) after birth if the birth weight is less or equal 1000g or 1 g/kg per day if birth weight is more than 1000g. The experimental group will begin treatment with 2 g/kg per day of 20% IVLE after birth. The IVLE dose in the control group will be increased by 0.5 g/kg per day daily until reaching 3 g/kg per day. The dose of IVLE will be increased directly from 2 to 3 g/kg per day the next day in the experimental group. Other macronutrients and micronutrients will be provided using the same products for amino acid and dextrose solutions in both groups. The maximum intake of amino acid will be 4 g/kg per day. The initial dextrose concentration in the parenteral nutrition (PN) will be 12.5%. The glucose infusion rate will be calculated and will be adjusted at the discretion of the attending neonatologist depending on the blood sugar levels. Total fluid intake will be started at 60 mL/kg per day for all infants. Monitoring for serum triglyceride will be performed after 24h of each lipid increment as per NICU policy in VLBW infants. This is part of routine care and not additional investigation. The serum triglyceride (TG) levels and other biochemical measurements such as serum electrolytes and acid-base status will be analyzed by the Calgary laboratory services at FMC. If hypertriglyceridemia occurs (>2.8 mmol/L, as per our current protocol), the IVLE concentration will be adjusted according to the following approved algorithm (Table 1).

Triglyceride Level (mmol/L)	Action
< 2.8	• Advance lipid intake as planned
2.8 – 4.5	• Reduce to previously tolerated dose
Greater than 4.5	• Stop lipid infusion for 24 hours

Table 1: Algorithm for adjusting IVLE in TPN.

Infants will be weighed every day on electronic scales with a precision of 2 grams by nursing personnel, using the In-Bed scale. Other anthropometric measurements such as length and head circumference will be taken by nursing personnel on admission and then weekly till discharge with a newborn length board and measuring tape respectively. Classification of newborns to define appropriate-for gestational age (AGA) status for infants at admission to the NICU will be based on Fenton's Growth Curves. Humidity in the incubators to minimize insensible water loss will be used as per our thermoregulation protocol for preterm and VLBW infants.

Data Collection and Outcome Variables:

Data collection will be completed by research assistant employed in the NICU. After the infants are enrolled, the neonatal-perinatal fellow or research assistant will collect the following information: maternal and neonatal demographic data, birth weight, gestational age at birth, daily weight, serum triglyceride levels, and other nutritional laboratory values during the days on PN, dose of IVLE, fluid intake, maximum percentage of weight loss (defined as: (birth weight−lowest postnatal weight)/birth weight× 100), and day of regaining birth weight. To determine the day of regaining birth weight, the infant should have 2 consecutive readings above the birth weight, then the first day of the 2 readings will be considered the day of regaining birth weight. The study team will collect clinical outcomes such as necrotizing enterocolitis (NEC) (Stage II and above according to Bell staging), BPD, intraventricular hemorrhage (IVH), ROP, death and EUGR. Survival free major morbidity (BPD, severe ROP, NEC and severe IVH) at discharge will be collected and analyzed. Data on neurodevelopmental outcome by 18-22 months corrected gestation for baby less than 29 weeks will be collected from the neonatal follow-up clinic. BPD will be defined as being dependent on oxygen at postmenstrual age of 36 weeks. Intraventricular hemorrhage will be defined based on ultrasound scans obtained before day 15 of life according to the classification of Volpe and Levene. EUGR will be defined for our study

as the presence of a measured weight below the 10th percentile at the time of hospital discharge on Fenton's growth Charts. Hyperglycemia will be defined as glucose level >10 mmol/L. Two registered dietitians will calculate fluids, calories and protein intakes and record the day of life when the infants achieved 100 and 120 ml/kg per day and age when PICC line is removed.

Sample Size and Statistical Analyses:

The primary statistical analysis will be to determine the effect of higher rates of parenteral fat intake on the maximum percentage of postnatal weight loss of the VLBW infants, during the first week of life. Independent, 2-sample, *t* tests will be used to compare the two groups for this primary outcome. Our previous data showed a maximum percent of weight loss in VLBW infants of: 11.4 (SD= 5.2). Drenckpohl et al. found that the weight loss in the first week was 8% only in the experimental group of VLBW infants who received higher dose of IVLE.[22] We considered 8% a reasonable percentage of weight loss in this category of infants and calculated our sample size to decrease our percentage by 3.4% (from 11.4% to 8%). Assuming an α value of 0.05 and a power of 0.80, a sample size of 76 infants (38 in each group) will be required.

Continuous variables such as days to achieve 90 kcal/kg per day, biochemical laboratory results, amount of lipid infused, and anthropometric results will be analyzed using independent, 2-sample *t* tests. Categorical variables such hypertriglyceridemia, proportions of EUGR infants, IVH, BPD and ROP will be evaluated using Pearson χ^2 tests.
All statistical tests will be 2-tailed, and the level of significance will be set at 0.05. All statistical analyses will be performed using STATA 11.1 (College Station, TX).

Feasibility and safety:
There are currently about 225 infants born at less than 1500 grams at FMC every year. With a 30% enrollment rate, the sample size will be reached in around 18 months. Halfway through enrollment, the overall rate of lipid intolerance will be reviewed. This will allow for a check for any unexplained sudden increase in incidence of lipid intolerance in relation to the study, or a significant reduction that may allow decreasing of the number needed to enroll. Neonatology section research assistant and study coordinator will help in recruiting and collecting the data.

Plans for dissemination or translation of results and plans for next steps in study of topic:
Findings from this study will generate insight into the effects and tolerance of high and early parenteral fat use in preterm infants. It will further provide answers whether the experimental regimen provides normal level of TG. The study will also set the basis to test the long term neurodevelopmental outcome for infants who received the new regimen of fat in the near future. If the results of the study indicate clinical benefit, this would provide evidence for generalizing the use of the new regimen routinely in the NICU.

Appendix:

	Early Aggressive group	**Comparison group**	
		≤1000 g	**>1000g**
Day 0	2 g/kg/d	0.5 g/kg/d	1 g/kg/d
Day 1	3 g/kg/d	1 g/kg/d	1.5 g/kg/d
Day 2	3 g/kg/d	1.5 g/kg/d	2 g/kg/d
Day 3	3 g/kg/d	2 g/kg/d	2.5 g/kg/d
Day 4	3 g/kg/d	2.5 g/kg/d	3 g/kg/d
Day 5	3 g/kg/d	3 g/kg/d	3 g/kg/d
Total	**17** g/kg	**10.5** g/kg	**12** g/kg

Difference in Lipid intake after 5 days: 5- 6.5 g/kg (≈50-65 KCal/kg).

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