Proactive Enteral Nutrition in Moderately Preterm Small for Gestational Age Infants: A Randomized Clinical Trial

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Objective To investigate the efficacy of a proactive feeding regimen (PFR) in reducing hospital length of stay in a population of moderately preterm small for gestational age (SGA) infants.

Study design SGA infants (*z*-score <−1.28) of gestational age (GA) 32-36 weeks and birth weight (BW) >1499 g were allocated at random to receive either a PFR, starting with 100 mL/kg/day and gradually increasing to 200 mL/kg/day by day 4, or a standard feeding regimen, starting with 60 mL/kg/day and gradually increasing to 170 mL/kg/day by day 9. All infants received human milk.

Results A total of 72 infants were randomized to the 2 groups, 36 to the PFR group (mean GA, 35.1 ± 0.7 weeks; mean BW, 1761 ± 177 g) and 36 to the standard feeding regimen group (mean GA, 35.5 ± 1.2 weeks; mean BW, 1754 ± 212 g). Infants in the PFR group were discharged significantly earlier (mean, 9.8 ± 3.1 days vs 11.9 ± 4.7 days; $P = .029$). The need for intravenous fluids (2.8% vs 33.3%; $P = .0013$) and the incidence of hypoglycemia (0 vs 33.3%; $P = .00016$) were significantly lower in the PFR group. Feeding intolerance and fecal calprotectin levels did not differ between the 2 groups.

Conclusion A PFR in moderately preterm SGA infants is well tolerated and significantly reduces both the length of stay and the risk of neonatal hypoglycemia. *(J Pediatr 2014;165:1135-9)*.

Small for gestational age (SGA) infants have increased neonatal morbidity and mortality, and are at increased risk for short stature, cardiovascular disease, insulin resistance, diabetes, dyslipidemia, and poor cognitive performance.[1] They also are predisposed to neonatal hypoglycemia because of reduced glycogen and fat stores, immaturity of hepatic enzymes, increased brain-to-body mass ratio, hyperinsulinism, and impaired ketogenesis.[2] It is often claimed that SGA infants require a greater energy supply than appropriate for gestational age infants.[3] This claim is true in the sense that SGA infants are predisposed to neonatal hypoglycemia, but is controversial with respect to growth. Animal studies have suggested that high nutrient intake (mainly high fat intake) after birth might be harmful after poor intrauterine growth, and may result in the metabolic syndrome.[4] Therefore, there is little agreement on how to feed SGA infants, the appropriate feeding volumes, and the rate of feeding advancement.[5] There is some evidence suggesting that a relatively more rapid advancement of enteral feedings in preterm infants could improve growth and decrease the need for intravenous (IV) infusions, without increasing the risk of necrotizing enterocolitis.[6,7]

The present study investigated the efficacy of a proactive feeding regimen (PFR) in reducing hospital length of stay (LOS) in a population of moderately preterm SGA infants.

Methods

This prospective randomized clinical trial was conducted between October 1, 2009, and March 31, 2013, in the neonatal intensive care unit of our university hospital, and was approved by our Institutional Review Board with parental consent. Preterm infants with gestational age (GA) 32-36 weeks, birth weight (BW) >1499 g, and weight *z*-score <−1.28 were eligible for inclusion into the study.

Infants with severely abnormal Doppler velocimetry findings in fetal vessels (ie, brain-sparing, absent, or reversed end-diastolic flow), major congenital anomalies, neonatal congenital infections, or severe birth asphyxia (Apgar score ≤5 at 10 minutes or mechanical ventilation, or need for resuscitation at 10 minutes or pH <7.0, or base deficit ≥16 in a cord blood or

BW	Birth weight
GA	Gestational age
IUGR	Intrauterine growth restriction
IV	Intravenous
LOS	Length of stay
PFR	Proactive feeding regimen
SFR	Standard feeding regimen
SGA	Small for gestational age

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arterial blood sample obtained within 1 hour of birth) were excluded from the study. Infants without data on Doppler velocimetry in fetal vessels were excluded as well.

Study infants were assigned at random to the PFR group or the standard feeding regimen (SFR) group within the first 3 hours of life. G.B. generated the allocation sequence using Stata 10 (StataCorp, College Station, Texas). L.M. and L.G. enrolled participants and assigned them to study groups by opening sealed envelopes. The randomization was stratified according to BW *z*-score (<-1.88 or ≥ -1.88) and GA (32-34 weeks or 35-36 weeks).

Outcomes and Sample Size Calculation

The sample size was calculated based on the primary outcome, which was the hypothesized lower LOS for the infants in the PFR group. A retrospective review of our database of a similar population of preterm SGA infants over the previous 2 years found a mean LOS of 14 ± 6 days. Calculations indicated a sample size of 36 infants in each group to yield 80% power (with $\alpha = 0.05$) for detecting a 4-day difference in LOS. Secondary outcomes were amount of weight loss, time to regain BW, incidence of metabolic abnormalities, and frequency and duration of IV infusion.

Feeding Protocol

Infants assigned to the PFR group were fed on the first day of life with 100 mL/kg/day of human milk, followed by 130 mL/kg/day on day 2, 165 mL/kg/day on day 3, and 200 mL/kg/day from day 4 to discharge from the unit. In the SFR group, feeding was started on the first day of life with 60 mL/kg/day of human milk and gradually increased to 170 mL/kg/day by day 9. The human milk used in the study came from the mother, or pasteurized pooled premature human milk was used when the mother's milk was insufficient or unavailable.

The mode of feeding was customized according to GA. Infants of 32-34 weeks GA were fed by continuous gastric feeding until day 7 of life, and by gavage or bottle/breastfeeding thereafter. Infants of 35-36 weeks GA were fed by continuous gastric feeding for the first 2 days of life, and subsequently shifted to gavage or bottle/breast feeding. Nurses were allowed to try bottle-feeding in any infant, regardless of the mode of feeding and the group allocation, to promote sucking ability and feeding improvement.

All infants received human milk (own mother's milk or donor milk), except for infants of 35-36 weeks of GA, who received, after the first week of life, a preterm formula when their own mother's milk was not available.

Monitoring and Definitions

Intrauterine growth restriction (IUGR) was defined as impaired growth and development of the embryo/fetus during pregnancy, detected by reduced fetal growth velocity measurements on serial ultrasound scans.[8] GA was determined by the best obstetric estimate based on the first day of the last menstrual period, prenatal ultrasound, and postnatal physical examination. Weight was measured daily by nursing personnel using digital scales accurate to 5 g. Additional anthropometric measurements were performed weekly by the same investigator (L.G.), following standardized procedures. Length was measured with a fixed headboard and movable footboard. Head circumference was measured at the maximal occipitofrontal circumference, using a nonstretchable tape accurate to the nearest millimeter.

To avoid errors associated with week-to-week observer variability and errors associated with repeated-measures analysis, rates of weight, head circumference, and length gain were calculated by fitting a linear regression model to each participant's data.[9] Weight, length, and head circumference were compared with intrauterine reference values[10] using *z*-scores. Growth performance was measured by calculating the *z*-score change from birth to discharge (Δz-score). Postnatal weight loss and days to regaining BW were calculated as well.

Feeding tolerance was evaluated based on the daily amount of gastric residual volume and the daily number of vomiting episodes. The criteria for reducing enteral feeding were a gastric residual volume >4 mL/kg after a single meal or a gastric residual volume >2 mL/kg after 3 consecutive meals, or more than 3 consecutive episodes of vomiting. Criteria for complete withdrawal of enteral feeding were a gastric residual volume >5 mL/kg after a single meal, abdominal distension with an increase in abdominal circumference of >2 cm in 24 hours, metabolic acidosis with pH <7.20 for more than 2 hours, hypoxia with PaO_2 <50 mm/Hg for more than 2 hours, and hypotension.

Hypoglycemia was diagnosed based on a blood glucose level <45 mg/dL. Preprandial blood glucose level was measured by a glucometer during the first 48 hours of life or until more than 2 blood glucose levels >45 mg/dL were recorded. Hypoglycemia detected by glucometer was always confirmed by the enzymatic method.[11] Hypoglycemia was managed as follows: For a preprandial blood glucose level <45 mg/dL, a supplemental meal was given, and blood glucose level was checked 60 minutes after eating. If preprandial blood glucose level was <35 mg/dL, a continuous IV glucose infusion was initiated. If blood glucose level was <25 mg/dL, a 2.5-mg/kg glucose bolus was administered. The goal of treatment was to maintain a plasma glucose concentration of 50 mg/dL.

Bilirubin monitoring and phototherapy were performed following local written guidelines for the management of hyperbilirubinemia in preterm infants.

Discharge criteria were as follows: full feeding competency (breast or bottle sucking), normal weight gain, axillary temperature $\geq 36.5^{\circ}C$ after 72 hours in an open crib, and no apneic episodes after 72 hours without caffeine.

For each child, a stool sample (approximately 1 g) was collected from the diaper on days 3 and 7 of life. Samples were stored immediately at $-20^{\circ}C$, and calprotectin concentration was measured by enzyme-linked immunosorbent assay (Calprest; Eurospital, Trieste, Italy) according to the manufacturer's instructions. In this assay, the upper reference limit in healthy adults supplied by the manufacturer was 50 μg/g.