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Randomized Trial of Exclusive Human Milk versus Preterm Formula Diets in Extremely Premature Infants

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Objective To compare the duration of parenteral nutrition, growth, and morbidity in extremely premature infants fed exclusive diets of either bovine milk–based preterm formula (BOV) or donor human milk and human milk-based human milk fortifier (HUM), in a randomized trial of formula vs human milk.

Study design Multicenter randomized controlled trial. The authors studied extremely preterm infants whose mothers did not provide their milk. Infants were fed either BOV or an exclusive human milk diet of pasteurized donor human milk and HUM. The major outcome was duration of parenteral nutrition. Secondary outcomes were growth, respiratory support, and necrotizing enterocolitis (NEC).

Results Birth weight (983 vs 996 g) and gestational age (27.5 vs 27.7 wk), in BOV and HUM, respectively, were similar. There was a significant difference in median parenteral nutrition days: 36 vs 27, in BOV vs HUM, respectively ($P = .04$). The incidence of NEC in BOV was 21% (5 cases) vs 3% in HUM (1 case), $P = .08$; surgical NEC was significantly higher in BOV (4 cases) than HUM (0 cases), $P = .04$.

Conclusions In extremely preterm infants given exclusive diets of preterm formula vs human milk, there was a significantly greater duration of parenteral nutrition and higher rate of surgical NEC in infants receiving preterm formula. This trial supports the use of an exclusive human milk diet to nourish extremely preterm infants in the neonatal intensive care unit. *(J Pediatr 2013;■:■-■).*

The health benefits of human milk for premature infants are significant and continue to be reported.[1,2] Premature infants receiving their own mother's milk have better feeding tolerance and a lower incidence of necrotizing enterocolitis (NEC) than those fed preterm formula.[3] Because not all mothers of premature infants produce sufficient milk to meet their infants' needs and some have medical contraindications, pasteurized donor human milk has emerged as an alternative for mother's own milk. It has been unclear, however, if pasteurized donor human milk confers the same health benefits as does mother's own milk.[4] Indeed, better feeding tolerance and fewer cases of NEC are reported in premature infants fed donor human milk compared with those fed formula, but those infants fed donor human milk had slower rates of growth and biochemical abnormalities suggestive of protein and mineral insufficiency.[5-7]

A randomized trial was conducted in extremely premature infants fed either pasteurized donor human milk or preterm formula as supplements if their own mother's milk supply was inadequate.[7] The results of this trial found that infants who received their own mother's milk had 50% less NEC and/or late-onset sepsis compared with infants fed either donor human milk or preterm formula. Importantly, there were no differences in morbidity between infants receiving supplements of either pasteurized donor human milk or preterm formula, but those receiving pasteurized donor human milk had slower growth. The diets in that study, however, were not derived exclusively from human milk; they contained bovine milk–based human milk fortifiers and the nutrient composition of the pasteurized donor human milk was not confirmed.

We previously reported the beneficial effects of an exclusive human milk diet (mother's own milk plus human milk–based human milk fortifier and supplementation only with pasteurized donor milk if needed) compared with a diet of mother's own milk plus bovine milk–based human milk fortifier and supplementation with bovine milk–based products.[8] That multicenter randomized trial reported significantly less NEC and surgery for NEC in infants receiving the exclusive human milk diet. Nearly 80% of the milk fed to study infants was their mothers' own milk so that benefits attributed only to donor human milk could not be ascertained fully.[8]

BOV	Bovine milk–based preterm formula
HUM	Human milk fortifier
NEC	Necrotizing enterocolitis

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It is impractical and unethical to assign mother's own milk diets by random allotment. The technology[9] enabling the provision of an appropriately fortified, exclusive human milk diet allowed for the design of a randomized trial of human milk vs formula in extremely premature infants whose mothers were unwilling or unable to provide their milk. We hypothesized that infants fed an exclusively human milk–based diet have better short-term health outcomes, designated as fewer days of parenteral nutrition and less morbidity, than similar infants fed only a bovine milk–based diet, without detrimental effects on growth.

Methods

Infants were enrolled from 7 neonatal intensive care units (6 were in the US and 1 was in Austria). Infants with birth weights of 500-1250 g whose mothers did not intend to provide milk were eligible if they received parenteral nutrition within 48 hours after birth and enteral feedings before 21 days of age. Infants were not enrolled if they had major congenital malformations, were transferred to a study site after 48 hours, had a high likelihood of transfer to a non–study institution during the study period, or were participants in another study affecting nutritional management. Randomization was performed separately for each study center. The investigators, patient care providers, and families were blind to group assignment.

Sample size was based on the primary outcome, duration of parenteral nutrition, an objective, quantifiable surrogate of feeding tolerance and neonatal morbidity.[8] The mean duration of parenteral nutrition in extremely premature infants in a study of formula-fed infants was 35 days with an SD of 22 days (Paula Meier, MD and Cynthia Blanco, MD, personal communication, February 2007). To demonstrate a 50% reduction in parenteral nutrition days in the human milk–based group, a sample size of 26 infants per group was needed for a 2-sided α error of 5% and power of 90%, which included a 10% adjustment for nonadherence to the protocol. The study was approved by the institutional review boards of each center, and written informed consent was obtained from the parents or legal guardians of all subjects before enrollment.

This was a blinded, randomized controlled trial in consecutive infants whose mothers did not intend to provide their milk. Blinding was handled by independent hospital personnel not associated with the care of the study infant, and milk was prepared away from the study infant's bedside, typically using masked feeding syringes with a colored covering. When enteral nutrition was initiated, enrolled infants were assigned to receive a bovine milk–based preterm formula (BOV) diet or an exclusive appropriately fortified human milk diet (HUM). The BOV diet consisted initially of 20 kcal/oz preterm formula and subsequently 24 kcal/oz strength. The HUM consisted of pasteurized donor human milk (20 kcal/oz Neo20; Prolacta Bioscience, Monrovia, California). A pasteurized donor human milk–based human milk fortifier (Prolact+ H^2MF; Prolacta Bioscience) was added to meet the nutritional needs for human milk fortification. Similar nutrition guidelines for initiation and weaning of parenteral nutrition (initiated within 48 hours of birth) and for the advancement and withholding of enteral feedings were followed at study sites. Trophic feedings were initiated 1-4 days after birth and were continued at 10-20 mL/kg/d as tolerated for up to 5 days. Subsequently, enteral nutrition volume was increased by 10-20 mL/kg/d. Decisions about increases in feeding volume, halting of feeding advancement, and fortification were made by the clinical team based on the same feeding guideline supplied to each site. The goals for enteral nutrition were 150 mL/kg/d and 120 kcal/kg/d.

Daily body weight and weekly recumbent length and head circumference were recorded. Growth was determined from the time the infant regained birth weight until the termination of the study. Study participation ended at the earliest of the following milestones: 91 days of age, discharge from the hospital (to home or to another hospital), or attainment of 50% oral feedings (ie, 4 complete oral feedings per day). The primary outcome of the study was the duration of parenteral nutrition. Secondary outcomes were growth, duration of hospital stay, days of mechanical ventilation and oxygen therapy, and the incidence of late-onset sepsis, NEC, and retinopathy of prematurity.

Late-onset sepsis was defined as clinical signs and symptoms consistent with sepsis occurring >5 days after birth in association with the isolation of a causative organism from a blood culture.[10] In cases of coagulase-negative *Staphylococcus*, ≥2 separate positive cultures were required. NEC was defined as Bell stage II disease or higher, and abdominal radiographs were read by radiologists unaware of study group assignment. At the conclusion of the study, all cases of NEC were reviewed in a blinded fashion by a panel of the study investigators. Furthermore, for any infant who did not complete the full follow-up study because of a transfer to another hospital or was otherwise removed from the trial, it was determined that no instance of NEC occurred. Feeding intolerance was defined by the following variables: gastric residuals >50% of the prior feeding or >2 mL/kg, bile- or blood-stained gastric residuals, emesis, abdominal distention or tenderness, changes in stool pattern or consistency, and presence of blood in the stool. Feeding intolerance was quantitated by the number of days that feedings were withheld. Weight gain was calculated for each subject as the slope of the regression of weight by age in days. For head circumference and length, velocity was calculated as the change over that time divided by the interval in weeks.

Statistical Analyses

The 2 study groups were compared using an intention-to-treat paradigm; any randomized infant remained in their group for the final analyses. Kaplan-Meier[11] estimates for the distribution of parenteral nutrition days were compared between study groups using the log-rank test. The Wilcoxon rank-sum test was used for univariate group comparisons. Categorical data were compared using the χ^2 test with the *P* value determined by an exact procedure (StatXact 7; Cytel Software Corporation, Cambridge, Massachusetts). Data are

Table I. Characteristics of study infants

	BOV	HUM
No.	24	29
Birth weight, g	983 ± 207	996 ± 152
Gestational age, wk	27.5 ± 2.4	27.7 ± 1.5
Small-for-gestational age, n	2 (8%)	3 (10%)
Male sex, n	11 (46%)	12 (41%)
Apgar score at 5 minutes <6, n	3 (13%)	0
Duration of hospital stay, d	82 (62, 124)	72 (64, 104)
Mean enteral intake, mL/kg/d*	82 ± 32	98 ± 29
First feeding, d	6.5 (3, 8)	4.0 (2, 7)
Time to full enteral feed, d	29.3 ± 14.7	24.6 ± 11.7
Feeding intolerance events, n	1.2 ± 1.3	1.1 ± 1.3
Weight gain, g/d	17 ± 7.1	15 ± 5.8
Head growth, cm/wk‡	0.88 ± 0.18	0.78 ± 0.26
Length gain, cm/wk†	1.12 ± 0.28	0.84 ± 0.21

Values are mean ± SD or median (25th, 75th percentiles).
*$P = .03$.
†$P = .006$.
‡Removing 1 infant with hydrocephalus.

presented as mean ± SD unless otherwise indicated (median ± IQR). Analyses were performed by an independent statistician and by the study group.

Results

We enrolled 53 infants (Figure 1; available at www.jpeds.com). The duration of the study was similar between BOV and HUM groups: 50 ± 23 vs 54 ± 20 days, respectively ($P = .65$). The groups had similar baseline characteristics (Table I), and there were no differences in race or ethnicity, receipt of antenatal steroids, or time to full enteral feedings. Growth rates were slightly less in HUM than in BOV infants, but only differences in recumbent length gain were significant (Table I). The groups differed in the duration of parenteral nutrition and the incidence of NEC and NEC requiring surgery (Table II and Figure 2). The 6 cases of NEC occurred on average at 29 days of age (range, 16-55 days), and the average amount of enteral feeding up to the diagnosis of NEC was 1762 mL (range, 14-3462 mL). After controlling for race, receipt of antenatal steroids, Apgar score, and age at first enteral feeding, a multivariate regression identified only exclusive human milk diet as significant ($P < .01$). Based on NEC surgery results, the number of infants needed to be fed an exclusive human milk diet to prevent 1 case of surgical NEC is 6 infants.

Table II. Clinical outcomes of study infants

	BOV	HUM
Parenteral nutrition, d*	36 (28, 77)	27 (14, 39)
Late-onset sepsis, n	19 (79%)	16 (55%)
NEC, n†	5 (21%)	1 (3%)
NEC surgery, n‡	4 (17%)	0
NEC and/or death, n†	5 (21%)	1 (3%)
Mechanical ventilation, d	24 (10, 75)	17 (2, 38)
Oxygen therapy, d	28 (21, 61)	20 (5, 32)
Retinopathy of prematurity, n	5 (21%)	8 (28%)
Death, n	2 (8%)	0

Values are median (25th, 75th percentile).
*$P = .04$.
†$P = .08$.
‡$P = .036$.

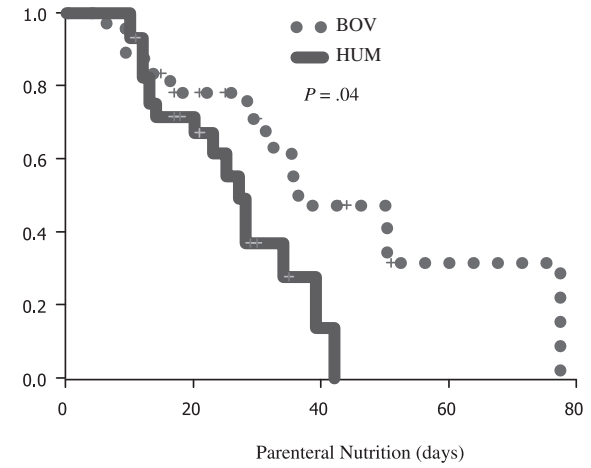

Figure 2. Proportion of infants receiving parenteral nutrition during study.

Discussion

Extremely preterm infants were fed an exclusive diet of appropriately fortified human milk or preterm formula. Infants fed the exclusive human milk diet required fewer days of parenteral nutrition and had significantly less morbidity than did similar infants fed preterm formula. Despite the small population studied, we found that the incidence of NEC was less and NEC requiring surgical intervention significantly less in the HUM group than in the BOV group. These data support those reported in our previous study of pasteurized donor human milk vs preterm formula used as supplements to a mother's own milk diet.[8]

The processing and preparation of an exclusive human milk diet require extensive technology for pasteurization and ultrafiltration to enable concentration of components to produce a human milk fortifier.[9] The original suggestion for making such a product comes from Lucas et al.[12] The technology has the potential benefits of concentrating bioactive factors and preventing exposure to bovine milk–based products. We did identify slightly slower growth in HUM vs BOV but believe that these small differences can be prevented by further adjustments in fortifier content to support improved rates of growth.

Reasons for the lack of availability of maternal breastmilk in this study included maternal exposure to medications or medical complications, anticipated absence of mother (including surrogacy, incarceration, and distance from hospital), and maternal use of illicit drugs. Some of these factors may contribute to a higher risk of NEC in the study population and make it especially important to have a human milk option for enteral nutrition.

In the entire study cohort, the incidence of NEC was 11.3%, which agrees with the rate reported from large

groups of similarly sized infants (Vermont Oxford Network, Burlington, Vermont). The control group had a rate of 21%, which realistically may represent the risk for a solely formula-fed baby of <1250 g birth weight. On the other hand, the 3% rate in the group exclusively fed human milk is in close agreement with that reported in the study by Sullivan et al.[8]

Thus, the data from these 2 randomized trials contribute significant knowledge to enable guidelines for the feeding of premature infants. Indeed, the recent American Academy of Pediatrics policy statement on the use of human milk states that premature infants should receive only human milk from their mother and that, if it is not available, pasteurized donor human milk should be used.[13] Furthermore, the US Surgeon General's Call to Action to Support Breastfeeding directly states that more research is needed and that the use of donor human milk should be increased.[14] In conclusion, the results of this study and other recent studies,[2,8] as well as the US national recommendations, mandate a greater need for enhanced lactation support in the neonatal intensive care unit as well as an imperative to establish more human milk banks. ■

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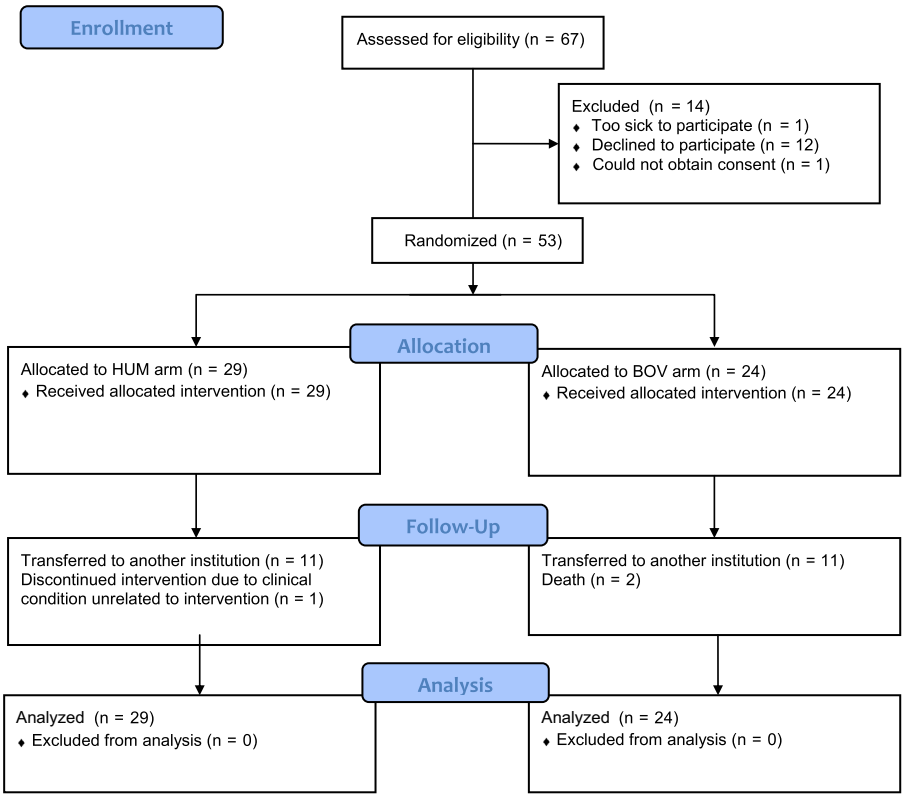

Figure 1. CONSORT flow diagram.