Original Research

international lactation consultant association®

Journal of Human Lactation
1–9

DOI: 10.1177/0890334419892908
journals.sagepub.com/home/jhl
SAGE

The Influence of Donor Milk Supplementation on Duration of Parenteral Nutrition in Preterm Infants

Bibiana Chinea Jiménez, PNP, PhD[1], Marta Cabrera Lafuente, MD, PhD[1], María L. Couce, MD, PhD[2], Rosario Madero[3], Maximo Vento, MD, PhD[4], Antonio Villarino Marín, PhD[5], and Miguel Saenz de Pipaon, MD, PhD[6]

Abstract

Background: Data are limited on the association between the use of donor human milk and improvements in feeding tolerance.

Objective: To determine the influence of the duration of parenteral nutrition on the growth and morbidity of the breastfed newborn when using donated human milk in the absence of mother's own milk.

Methods: We conducted a retrospective study before and after the intervention that compared two groups of newborns ($N = 284$; each group $n = 142$). We used a convenience sample of all newborns ≤32 weeks gestation consecutively admitted in a single unit before (Group 1 between December 2012 and May 2014) or after (Group 2 between October 2014 and December 2016) the availability of donor human milk. In Group 2, donor human milk was administered at least 3 to 4 weeks or until the baby weighed 1,500 g. Weight was recorded daily and length and head circumference weekly. Parenteral nutrition was continued until enteral feeding volume reached 120 ml/kg/day. Additional variables measured were the number of days with a central venous catheter, age that the enteral feeding volume reached 150 ml/kg/day, and duration of stay.

Results: The duration of parenteral feeding was the same before and after: 12 (8.23) and 11 (7.19) days ($p = .822$). The *z* scores for weight and height of newborns was lower in Group 2 = −1.8 (1.0) and −2.3 (1.1) and Group 1 = −1.2 (1.1) ($p < .001$) and −1.8 (1.4) ($p = .005$).

Conclusion: We did not find an association between the administration of donor human milk as a supplement to mother's own milk and reduced number of days of parenteral nutrition.

Back translation by Laurence Grummer-Strawn

Keywords

breastfeeding, human milk, infant growth, infant nutrition, milk bank

Resumen

Antecedentes: existen datos limitados que asocian el uso de la leche humana donada con la mejora en la tolerancia a la alimentación.

Objetivo de la investigación: determinar la influencia de la duración de la nutrición parenteral en el crecimiento y la morbilidad del lactante cuando se usa leche humana donada en ausencia de la leche de la propia madre.

Métodos: Realizamos un estudio retrospectivo pre/post a la intervención que comparó dos grupos de recién nacidos (N=284; cada grupo n=142). Una muestra de conveniencia de todos los recién nacidos ≤32 semanas de gestación ingresados consecutivamente en una sola unidad antes (Grupo 1 entre diciembre de 2012 y mayo de 2014) o después (Grupo 2 entre octubre de 2014 y diciembre de 2016) de la disponibilidad de leche humana donada. En el Grupo 2, la leche humana donada se administró durante al menos 3–4 semanas o hasta que el lactante pesó 1500g. El peso se registró diariamente, y la longitud y el perímetro cefálico semanalmente. La nutrición parenteral se mantuvo hasta que el volumen de alimentación enteral alcanzó 120 ml/kg/día. Las variables adicionales medidas fueron el número de días con catéteres venosas centrales, la edad en que el volumen de alimentación enteral alcanzó 150 ml/kg/día y la duración del ingreso.

Resultados:el número de días de nutrición parenteral fue el mismo antes y después: 12 (8,23) y 11 (7,19) días (p = 0,822). Las puntuaciones z de peso y talla para los recién nacidos al alta fueron menores en el Grupo 2, -1.8 (1.0) y -2.3 (1.1), mientras que en el Grupo 1, -1.2 (1.1) (p <0.001) y -1.8 (1.4) (p = 0,005).

Conclusiones:no encontramos asociación entre la administración de la leche humana donada como suplemento a la leche materna de la propia madre y la reducción de días de nutrición parenteral.

Abstract by Bibiana Chinea Jiménez

Background

Human milk is considered the best feeding option to support growth and development of healthy term infants through the first 6 months after birth (Pecoraro et al., 2017). Feeding policy is crucial in health care management for preterm infants because early undernutrition may have long-term consequences (Su, 2014). Human milk may also offer substantial advantages to preterm infants; however, breastfeeding (including milk expressed) in these cases may not be feasible, or mother's own milk (MOM) may not be available or in sufficient amount. Under these circumstances, feeding with donor human milk (DHM) and/or preterm infant formula are the only available options. The World Health Organization (2018) recommended DHM be used preferentially over formula for low-birth-weight infants.

Protection against necrotizing enterocolitis (NEC) is the main clinical benefit derived from the use of DHM rather than formula (Herrmann, 2014). Limited data associate use of DHM with improvement in feeding tolerance (ESPGHAN Committee on Nutrition et al., 2013). An important putative benefit of DHM is that the delivery of immune-protective and growth factors to the immature gut mucosa may improve feeding tolerance. Parenteral nutrition in very-low-birth-weight (VLBW) infants is started immediately after birth and continued until full enteral feeding is achieved. Parenteral nutrition duration is related to feeding tolerance (Cristofalo et al., 2013).

DHM is usually obtained from mothers who have delivered at term and provides less protein and fewer minerals than MOM (Ballard & Morrow, 2013). Macronutrient content of human milk changes during lactation and has significant interindividual variability. Despite routine use of human milk fortifiers on MOM and DHM, it may be necessary to further fortify DHM with extra macronutrients (especially protein) due to lower content. Adjustable fortification is appropriate for stable preterm infants and is practical and feasible (Kadıoğlu Şimşek et al., 2019). Blood urea levels are used to modify fortifier concentration.

This situation may be more complex for human milk oligosaccharides (HMOs). Premature infants who receive MOM have lower rates of NEC and sepsis. This is likely due to HMOs. Diversity and levels of HMOs that contain fucose or sialic acid are lower in mothers delivering preterm (Underwood et al., 2015).

Key Messages

- There are limited data that associate the use of donor human milk with better feeding tolerance.
- There is no reduction in the number of days of parenteral nutrition and days with central venous catheter associated with the use of pasteurized donor human milk to supplement mother's own milk.
- The time needed for very-low-birth-weight infants to achieve targeted full enteral feedings was similar whether mother's own milk was supplemented with donor human milk or preterm formula.
- Support efforts should focus on helping mothers to provide their own milk to their infants.

We hypothesized that VLBW infants fed DHM with fortifier as a supplement to MOM, rather than formula, would achieve feeding goals earlier and therefore require fewer days of parenteral nutrition without measurable detrimental influences on growth. The research aim was to determine the influence of DHM on parenteral nutrition duration (primary outcome), growth, and morbidity when used in absence of MOM.

Methods

Design

This was a retrospective pre/postobservational study designed to compare two cohorts born before (Group 1) and after (Group 2) the introduction of DHM with fortifier as a supplement to MOM; previously, formula was the supplement used. The ethics committee of La Paz University Hospital approved the study design.

Setting

We conducted the study in the NICU of La Paz University Hospital (Madrid, Spain). Nutritional policy in our unit is as

[1]Department of Neonatology, Hospital Universitario La Paz, Madrid, Spain
[2]Diagnosis and Treatment of Congenital Metabolic Diseases Unit, Department of Neonatology-Pediatrics, IDIS, CIBERER, University Hospital Clinic of Santiago de Compostela, Santiago de Compostela, Spain
[3]Department of Biostatistics, Hospital Universitario La Paz, Madrid, Spain
[4]Division of Neonatology, University & Polytechnic Hospital La Fe, Health Research Institute La Fe, Neonatal Research Group, Valencia, Spain
[5]Facultad de Enfermería, Fisioterapia y Podología, Universidad Complutense de Madrid, Madrid, Spain
[6]Department of Neonatology, Hospital Universitario La Paz, Red de Salud Materno Infantil y Desarrollo – SAMID, Universidad Autónoma de Madrid, Madrid, Spain

Date submitted: June 19, 2018; Date accepted: November 13, 2019.

Corresponding Author:
Miguel Saenz de Pipaon, Department of Neonatology, Hospital Universitario La Paz, Pº de la Castellana 261, Madrid, 28046, Spain.
Email: miguel.saenz@salud.madrid.org

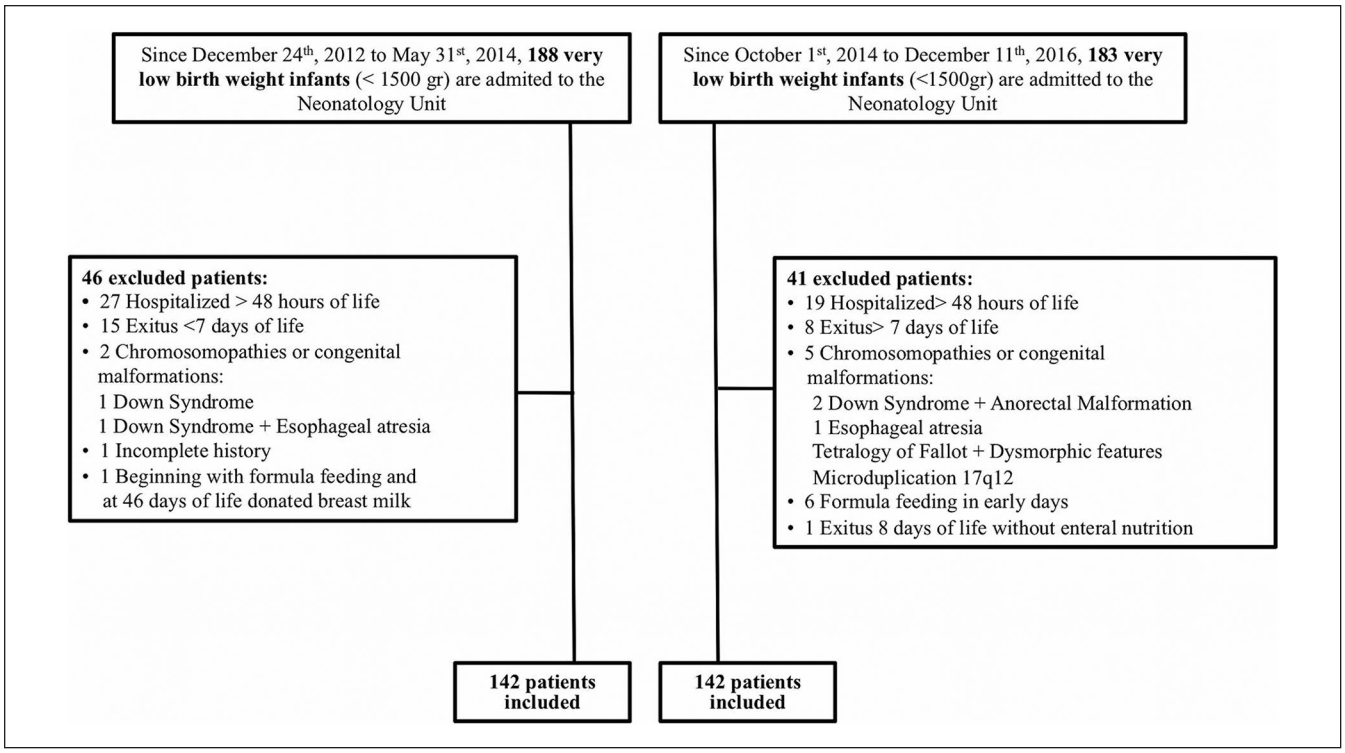

Figure 1. Progress of very low-birth-weight infants through phases of recruitment comparing donor milk with preterm formula as a supplement to mother's milk.

follows: Amino acid solution (Primene; Clintec Benelux NV, Brussels, Belgium) is started immediately after birth at 2.5 g/kg/day and increased to 3.5 g/kg/day. Glucose infusion is started at an initial rate of 5 mg/kg/min and is increased daily according to glucose tolerance, targeting serum glucose of 90 to 150 mg/dl. Parenteral lipid emulsion is initiated on Day 2 at 1 to 2 g/kg/day and increased to 3 g/kg/day while maintaining a serum triglyceride level <200 mg/dl.

Most infants received partial MOM feeding. Less than 5% of infants receive only MOM from birth to discharge, and less than 25% are discharged on exclusive MOM. Nurses and doctors have training in human milk feeding support. Mothers are encouraged to pump frequently and early after birth, whatever the gestational age of the baby. Prolonged skin-to-skin contact between parents and the newborn for extended periods, as kangaroo care, is supported. There are no lactation support providers to help moms.

Sample

Eligible participants were all preterm infants ≤ 32 weeks gestational age, with a birth weight of $<1{,}500$ g. Infants were grouped according to DHM availability. Group 1 included all infants that met inclusion criteria admitted from December 24, 2012, to May 31, 2014, before DHM was available as a supplement to MOM. Group 2 included all infants that met inclusion criteria admitted from October 1, 2014, to December 11, 2016, beginning 4 months after DHM was available. No significant changes to clinical practice and policies occurred during the study period.

Exclusion criteria were: genetic diseases, including chromosomopathies; major malformations; participants who did not receive enteral nutrition; incomplete data medical records; participants admitted after 48 hours of life; participants deceased in the first 7 days of life; and in Group 2, participants who received formula milk. Two hundred eighty-four infants were included. Sample size was based on number of days of parenteral nutrition, which was the primary outcome. The average parenteral nutrition need in VLBW infants was 16 days with a standard deviation of 6 days. To demonstrate a 10% decrease (2 parenteral nutrition days) during the period when DHM was available, a sample size of 142 infants per group was needed for an alpha level of 95%, and a beta risk (i.e., the power of the analysis) was chosen at 0.2 (meaning a power of 80%). Figure 1 shows a flow diagram describing eligibility, recruitment, and participants included in final assessment.

Measurement

The primary outcome examined by this study was duration of parenteral nutrition, an objective, quantifiable surrogate of feeding tolerance designated as days of parenteral nutrition. Parenteral nutrition was maintained until infants' feeding

tolerance reached 120 ml/kg/day. Secondary outcomes were number of days with central lines; number of days after birth at which 150 ml/kg/day of enteral nutrition was tolerated; growth at time of discharge from the hospital, measured as actual weight, length, and head circumference; duration of hospital stay; and the incidence of bronco pulmonary dysplasia (BPD), persistent ductus arteriosus (PDA), NEC, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), and late-onset sepsis (LOS). Discharge criteria and practices did not change between these two periods. Discharge criteria included the assessment of the patient's stable medical status without any concurring acute illness. Readiness for discharge included maintain normal body temperature in an open crib, demonstrate mature oral (suction/swallowing) feeding skills, appropriate weight gain, and maturity of respiratory control.

Morbidity definition and measurement. PDA was only considered if treatment (pharmacological/surgical ligation) was reported (Ledo et al., 2017). Moderate-severe BPD was considered (Higgins et al., 2018). LOS was defined as positive blood culture obtained after 72 hours of life (Stoll et al., 2002). IVH was defined as Papile's grade >2 (Papile et al., 1978). Infants underwent scheduled examinations and were graded according to the international classification of retinopathy of prematurity. NEC was defined as neumatosis intestinalis (Bell et al., 1978).

Infants' body weight was recorded daily. Measurements were taken at an electronic weighing bascule (Seca, Hamburg, Germany), precise to a 10-g resolution. Length was obtained weekly by an infant stadiometer, precise to the nearest 0.1 cm (Seca 210, Seca, Hamburg, Germany). Head circumference measurement was obtained weekly with a measuring tape, precise to the nearest millimeter. Study participation ended at discharge from the hospital. The *z* scores were calculated for gestational/postmenstrual age and gender according to Fenton and Kim's (2013) growth references. Weight gain was calculated according to the method described by Patel et al. (2005) and expressed as g/kg/day. Linear and head growth rate were expressed as cm/week.

The same nutrition and fluid protocol were in force during both periods of time included in the study. Enteral nutrition was introduced in the first 24 hours postnatal. The neonatologist in charge made daily decisions about increasing the volume of feeding, halting the feeding progress, and fortification based on feeding guidelines, gastric residuals, vomiting, and abdominal distension. The goal for enteral nutrition was to reach 150 ml/kg/d. DHM was administered to infants until ≤32 weeks gestation, at least 3 to 4 weeks of postnatal age, or 1,500 g body weight was achieved, whichever came last. After reaching that milestone when enough maternal human milk was not available, preterm infant formula was fed. DHM was given to all infants whose parents signed informed consent and only when MOM was not available. In both study periods, human milk was fortified with a bovine milk fortifier, 5% FM 85 (Nestle, Munchen, Germany), initiated as soon as enteral feeding volume reached 100 ml/kg/day for all preterm infants born before 34 weeks gestation and who were fed either MOM or DHM. Adjustable fortification, based on infant blood urea nitrogen analysis, was used with four different levels using FM 85 (Nestle, Munchen, Germany) at 5% (5g/100 ml of HM) and 6.25% and if needed, addition of bovine protein concentrate at different concentrations (0.4 g and 0.8 g/100ml) (Arslanoglu et al., 2006). Nutritional information from DHM milk analysis was not considered for human milk fortification (Rosas et al., 2016).

In general, for a lactating person to be able to donate milk, at least 2 or 3 weeks must have elapsed since they gave birth, and breastfeeding or pumping must be well established. Human milk extraction was done manually or with a manual or electric breast pump. Each extraction was stored in a glass container, identified with a label and the name of the donor. A separate container was used for each extraction. The container was immediately frozen after extraction, at −20° C. The human milk was taken to the milk bank within a maximum period of 15 days. Donated human milk was stored frozen between −20° C and −30° C.

The nutritional content (protein concentration and energy content) was also analyzed. The classic Holder method was used for pasteurization at 62° C for 30 minutes. The sterility was checked by pasteurized milk culture. After the sample was taken, the DHM was frozen again in aliquots of 30, 60, 120, or 240 ml. By not mixing milk from different donors, traceability from donor to recipient was maintained.

Three situations are described in each group. exclusive MOM, exclusive formula or mixed, and MOM and formula, including those receiving some human milk and some formula. Because data on consumption of milk during the entire hospital stay were not complete for all infants in Group 1, history of nutrition from birth to discharge is not reported. None of the infants in Group 2 received formula during the first weeks of life.

Data Collection

Selection periods were from December 24, 2012, to May 31, 2014 (Group 1, G1), and from October 1, 2014, to December 11, 2016 (Group 2, G2). Infants born between May 31, 2014, and October 1, 2014, were not selected because we assumed that adhesion to the protocol was fully operative 4 months after DHM was available.

Parental consent was obtained for the use of DHM. The hospital ethics board did not consider it necessary to obtain informed consent for collecting data because DHM was introduced for routine therapy and the control group data were collected retrospectively while data from the experimental group were collected prospectively by the same researcher (B.C.J.). Data were anonymized and the data kept encrypted.

Table 1. Characteristics of the Sample ($N = 284$).

Characteristics	Group 1 ($n = 142$) *M* (*SD*)	Group 2 ($n = 142$ *M* (*SD*)	*p*
Gestational age at birth, weeks	28.7 (2.6)	28.8 (2.7)	.782
Birth weight, grams	1,060 (263)	1,031 (253)	.340
Weight-for-age z score at birth	−0.33 (0.98)	−0.48 (1.03)	.185
Length at birth, cm	36 (3)	36 (4)	.504
Length-for-age z score at birth	−0.45 (1.17)	−0.61 (1.46)	.304
Birth head circumference, cm	25 (2)	25 (2)	.695
Head-circumference-for-age z score at birth	−0.37 (1.12)	−0.50 (1.07)	.312
Apgar score at 1 min	6 (5.8)	6 (5.8)	.326
Apgar score at 5 min	8 (7.9)	8 (7.9)	.082
Apgar score at 10 min	8 (8.9)	7 (6.8)	.009
Mother's age (years)[a]	34 (6)	34 (6)	.977

Note: Gestational age determined using maternal estimates of last menstrual period. If early ultrasound prediction differed by 2 weeks or more, the gestational age estimate derived from early ultrasound was used.
[a]Missing values = 1.

Data Analysis

Descriptive results are expressed as mean (standard deviation) or median (range) or percentage. Bivariable analysis was done with two-tailed chi-square or *t* test, as appropriate. ANOVA has been used to compare means between more than two groups. We used a multivariable linear regression model to test which period (independent variable) was independently associated with the duration of parenteral nutrition among VLBW infants (dependent variable). The association between availability of DHM and duration of parenteral nutrition was corrected for birth weight, gestational age, and different clinical characteristics at birth, not outcomes that occurred later in the clinical course (independent variables).

To exclude the effect of early infant formula feeding on growth outcomes, infants in G1 who received exclusively MOM with human milk fortifier, 5% FM 85 (Nestle, München, Germany); those who received MOM with human milk fortifier, 5% FM 85 (Nestle, München, Germany) and formula; and those who received only formula were compared with G2 independently. We adjusted our alpha level of 95%. Statistical analyses were done using SAS system software Version 9.3.

Results

Both groups had similar baseline characteristics (Table 1). Percentage of small for gestational age infants was similar in both groups: $n = 16$ (11%) and $n = 22$ (16%) in G1 and G2, respectively. Gender was also similar between G1 and G2: $n = 70$ (49%) and $n = 72$ (51%) females in each group. Multiple births and cesarean section percentages were similar in both groups.

All participants in G2 received DHM as a supplement to MOM if necessary. No statistical difference was found between groups in the duration of parenteral nutrition (G1 vs. G2, median = 12 [0–151] vs. 11 [0–120] days), days with central lines, postnatal age at which 150 ml/kg/day enteral volume of feed was reached, or time to full oral feedings (Figure 2). In the multivariable linear regression analysis, birth weight, not DHM, was significant on duration of parenteral nutrition (Table 2). All participants received 150 ml/kg/day, and target fortification protocol was followed. There was no statistically significant difference between G1 and G2 in length of stay ($M = 70$, $SD = 34$ vs. $M = 68$, $SD = 34$ days, respectively). Participants in G1 and G2 started with enteral feeds on day $M = 3.4$ ($SD = 4.1$) and day $M = 2.2$ ($SD = 2.4$), respectively ($p = .003$).

At discharge, G2 had significantly lower weight, length, and head circumference than G1. When these measurements were expressed as *z* scores, G2 still had lower weight and length at discharge (Table 3). Fall in weight *z* score from birth to discharge was higher in G2 than in G1 ($M = -1.275$, $SD = 0.077$ vs. $M = -0.894$, $SD = 0.077$, respectively; $p = .001$). There were no significant differences between G1 and G2 in weight gain ($M = 14$, $SD = 2$ vs. $M = 15$, $SD = 8$ g/kg/day; $p = .103$) or linear ($M = 0.9$, $SD = 0.3$ vs. $M = 1$, $SD = 0.6$ cm/week; $p = .279$) and head growth rate ($M = 0.8$, $SD = 0.2$ vs. $M = 0.9$, $SD = 0.5$ cm/week; $p = .145$). To analyze further differences in growth between G1 and G2, exclusive human milk feeding, human milk and formula mix feeding, and exclusive formula feeding participants in G1 were compared with participants in G2 who did not receive formula during the first weeks of life. Lower weight and length at discharge in G2 remained unchanged in a sensitivity analysis comparing exclusive human milk feedings in G1 with all the infants in Group 2 regarding growth during initial hospitalization. We selected in this analysis only participants in whom we were able to retrieve feeding at discharge (135 infants in G1; 142 infants in G2).

At discharge, more participants in G1 ($n = 61$, 45%) were exclusively fed MOM than those in G2 ($n = 50$, 35%;

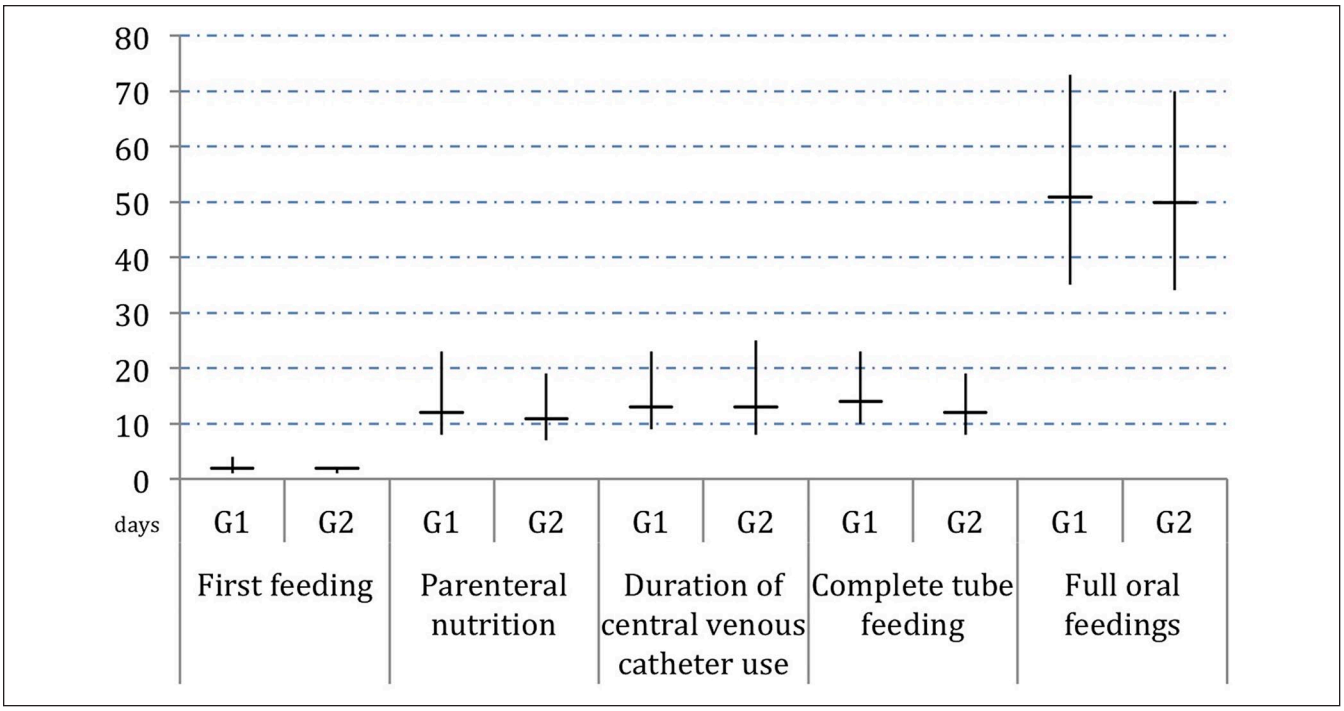

Figure 2. Parenteral nutrition duration and feeding tolerance. All values expressed as median (p25, p75).
G1 = Group 1: before donor human milk policy; G2 = Group 2: after the availability of donor milk.

Table 2. Multivariable Linear Regression Model for Normalization of Duration of Parenteral Nutrition.

Variables	Beta	SE (Beta)	*p*
Group	−1.686	1.670	.314
Birth weight	−0.024	0.004	<.001
Gestational age, birth	0.036	0.443	.935
Apgar score (5 min)	1.123	1.227	.361
Apgar score at 10 min	−2.064	1.400	.142
Constant	52.037	10.420	<.001

$p = .049$) (Figure 3). No statistical differences were observed between G1 and G2 when participants were exclusively fed MOM at discharge in <28 weeks ($n = 24$ [45%] vs. $n = 19$ [31%]; $p = .206$) or ≥28 weeks ($n = 41$ [46%] vs. $n = 30$ [38%]; $p = .356$) when these groups were studied independently. In a preplanned exploratory analysis of individual morbidities, fewer participants in G1 had moderate to severe BPD than in G2 (Table 4).

Discussion

The outcome of our study was that VLBW infants needed similar time to achieve targeted feeding tolerance of full enteral feedings when MOM was supplemented either with the use of fortified donor milk or preterm formula. We did not find differences between the studied groups in the duration of parenteral nutrition or days of central venous lines, which were examined as surrogates for feeding tolerance. Ten percent of infants in both groups received only MOM during hospital stay; the percentage is low and similar between groups and does not change conclusions of the study. These results are consistent with those reported by Vázquez-Román et al. (2014). These researchers did not find significant differences in clinical markers of feeding intolerance (gastric residuals, spitting, abdominal distension, etc.) between preterm infants fed fortified human milk and those exclusively fed preterm formula. There are no conclusive data regarding improved feeding tolerance with human milk versus formula or DHM.

There are several possible explanations for the lack of improvement in feeding tolerance when supplementing with pasteurized donor human milk. First, heat treatment alters biological components, for example, growth factors (epidermal growth factor, transforming growth factor, insulin growth factor 1), lactoferrin, myoinositol, antioxidants, lactadherin, mucins, soluble CD4 and hormones (leptin; ESPGHAN Committee on Nutrition et al., 2013; Meier et al., 2017).

Second, both DHM and MOM need fortification (Radmacher & Adamkin, 2017). The use of fortifiers derived from cow's milk may interfere with human milk and its biological advantages in VLBW infants. Hence, bovine products may negatively influence gut epithelium integrity (Abdelhamid et al., 2013).

No differences in nutritional protocol between both time periods exist. Following that protocol, feeding tolerance of 120 ml/kg/day and parenteral nutrition discontinuation

Table 3. Infant Growth Outcomes ($N = 248$).

Outcomes	Group 1 ($n = 142$) *M* (*SD*)	Group 2 ($n = 142$) *M* (*SD*)	*t*	*p*
Postmenstrual age at discharge (weeks)	39.2 (3.6)	39.0 (3.5)	0.577	.578
Weight at discharge (kilograms)	2.701 (0.669)	2.421(0.666)	3.526	<.001
Weight-for-age z score at discharge	−1.2 (1.1)	−1.8 (1.0)	4.031	<.001
Length at discharge (centimeters)	45 (4)	44 (4)	2.882	.004
Length-for-age z score at discharge	−1.8 (1.40)	−2.3 (1.11)	2.821	.005
Head circumference at discharge (centimeters)[a]	33 (3)	32 (3)	2.059	.040
Head-circumference-for-age z score at discharge	−0.6 (1.4)	−0.9 (1.2)	1.529	.128

[a]Missing values = 2.

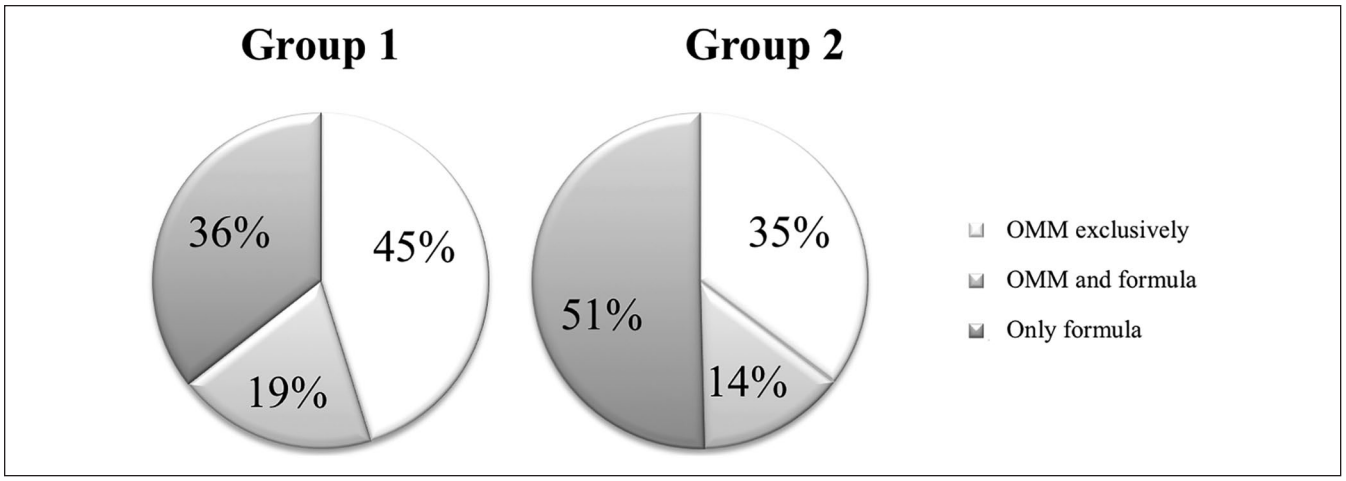

Figure 3. Infant feeding at the time of hospital discharge before (Group 1) and after (Group 2) donor human milk availability. Type of milk in percentage: mother's own milk (MOM) exclusively, only formula, or MOM and formula.

Table 4. Infant Morbidities in the Sample ($N = 284$).

Morbidities	Group 1 ($n = 142$) *n* (%)	Group 2 ($n = 142$) *n* (%)	*t*	*p*
Death	9 (6.3)	10 (7)	0.056	.812
Oxygen at 36 weeks	58 (41)	84 (59)	5.001	.034
IVH	48 (34)	38 (27)	1.668	.245
PDA	62 (44)	64 (45)	0.057	.905
NEC Stage ≥II	8 (6)	16 (11)	2.913	.134
Surgery	5 (4)	9 (6)	1.202	.412
ROP	34 (24)	38 (27)	2.298	.683

Note: IVH = intraventricular hemorrhage; PDA = patent ductus arteriosus; NEC = necrotizing enterocolitis; ROP = retinopaty of prematurity.

would be achieved at 7 days, quite sooner than the median number of days of parenteral nutrition observed in Groups 1 and 2 (11 and 12 days, respectively). Initiation of enteral feeding is earlier by protocol if human milk is available, as is the case with donor human milk availability. Although no differences in basal characteristics exist between both groups (only for Apgar score at 10 min), infants in G2 showed lower *z* scores at birth. Earlier growth deficit may predispose to lower growth at discharge if protocol is not modified.

Infants in G1 had greater weight, length, and head circumference at discharge and lower fall in weight *z* score, "a more rational definition of postnatal growth restriction" (Zozaya et al., 2018). Even though in this group, a smaller percentage of infants were exclusively fed formula at discharge, no statistical differences were found in weight, length, and head circumference gain. The *z* scores allow better comparisons between different gestational ages and genders due to their comparison with their own references. In

multiple other studies, slower growth has been observed in VLBW infants fed with DHM versus MOM (Vázquez-Román et al., 2014). The results of our study are consistent with those reported by Schanler (2005), which indicated that extremely preterm infants with insufficient MOM available who received DHM with fortifier had a slower rate of increase in weight. DHM is often provided by mothers of term infants who are more than 1 month postpartum, so DHM is likely to have lower protein content than would be ideal for nutrient requirements after standard fortification. Lipid globule as well as lipases and proteases can be altered with freeze-thaw cycles. Holder technique may partially data growth at discharge in VLBW infants receiving DHM. Nutritional information from DHM milk analysis was not considered for human milk fortification. To improve growth in DHM-fed infants, higher concentration of DHM fortification should be tested. MOM versus DHM intake may explain the differences given that they remained even in the subgroup discharged with MOM exclusively in G1 versus the whole G2. Although, infants receiving formula as early feeding may belong to one of the three subgroups in G1.

A higher incidence of BPD was found in G2, after availability of DHM. Whether this is due to less weight gain or related to reduced or absent components in DHM with fortifier that are present in MOM and may reduce BPD (e.g., antioxidants) cannot be answered with our study design (Assad et al., 2015; Panczuk et al., 2016). MOM feedings was associated with a reduction in BPD; however, the study was not designed to evaluate BPD as a primary outcome. The benefits of human milk feeding are difficult to study. However, there is a need for multicenter studies in relation to effect of DHM in morbidities and health care costs.

MOM intake at discharge deserves further consideration. During the study period, DHM acted more as a replacement than as a bridge to MOM. Recent reports suggested that the introduction of DHM does not reduce MOM intake (Kantorowska et al., 2016; Williams et al., 2016). However, our results are consistent with those of Esquerra-Zwiers et al. (2016), who observed a decrease in the MOM received by infants after the introduction of DHM. Only 4 months lapsed between G1 and G2, after DHM became available. No additional lactation support or increased training were initiated during this time. We suggest that there is room for improvement in lactation support to increase availability of MOM. "NICU care providers must frame the argument for the superiority of MOM over DHM with families, peers and hospital administrators in a manner that results in high doses and longer exposure periods for MOM use in VLBW infants" (Meier et al., 2017, p.).

Limitations

The intervention was not randomized; therefore, no generalization of our findings is possible. The sample includes nearly all infants admitted in each study period and so accurately represents the population. Nevertheless, infants in G1 were sicker and smaller than infants in G2, which may, in part, explain the lack of efficacy of the intervention shown in this study. Second, we compared two groups of participants during different time periods, so we cannot rule out that results may have been influenced by other alterations in the clinical practices of the unit. Third, fortification was not modified in DHM intake compared with MOM. It was not feasible to avoid the use of bovine products in fortification. Fourth, lactation technologies to improve the availability of MOM were not implemented concomitantly with the availability of DHM. Finally, the exact amount of DHM and MOM during the overall hospital stay consumed by each infant as well as daily caloric intake were not available.

Conclusions

DHM may decrease availability of MOM. Support efforts should focus on improving any and exclusive breastfeeding at discharge. Additionally, improvement in pasteurization techniques may lead to preservation of relevant biological factors in DHM that would contribute to increased feeding tolerance and earlier achievement of targeted enteral feeding volume.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Bibiana Chinea Jiménez https://orcid.org/0000-0003-3655-9423

References

Abdelhamid, A. E., Chuang, S. L., Hayes, P., & Fell, J. M. (2013). Evolution of in vitro cow's milk protein-specific inflammatory and regulatory cytokine responses in preterm infants with necrotizing enterocolitis. *Journal of Pediatric Gastroenterology and Nutrition*, *56*(1), 5–11.

Arslanoglu, S., Moro, G. E., & Ziegler, E. E. (2006). Adjustable fortification of human milk fed to preterm infants: Does it make a difference? *Journal of Perinatology*, *26*(10), 614–621.

Assad, M., Elliott, M., & Abraham, J. (2015). Decreased cost and improved feeding tolerance in VLBW infants fed an exclusive human milk diet. *Journal of Perinatology*, *36*(3), 216–220.

Ballard, O., & Morrow, A. L. (2013). Human milk composition: Nutrients and bioactive factors. *Pediatric Clinics of North America*, *60*(1), 49–74.

Bell, M., Ternberg, J., Feigin, R., Keating, J., Marshall, R., Barton, L., & Brotherton, T. (1978). Neonatal necrotizing enterocolitis. *Annals of Surgery*, *187*(1), 1–7.

Cristofalo, E. A., Schanler, R. J., Blanco, C. L., Sullivan, S., Trawoeger, R., Kiechl-Kohlendorfer, U., Dudell, G., Rechtman, D. J., Lee, M. L., Lucas, A., & Abrams, S. (2013). Randomized trial of exclusive human milk versus preterm formula diets in extremely premature infants. *The Journal of Pediatrics*, *163*(6), 1592–1595.

ESPGHAN Committee on Nutrition, Arslanoglu, S., Corpeleijn, W., Moro, G., Braegger, C., Campoy, C., Colomb, V., Decsi, T., Domellöf, M., Fewtrell, M., Hojsak, I., Mihatsch, W., Mølgaard, C., Shamir, R., Turck, D., & van Goudoever, J. (2013). Donor human milk for preterm infants. *Journal of Pediatric Gastroenterology and Nutrition*, *57*(4), 535–542.

Esquerra-Zwiers, A., Rossman, B., Meier, P., Engstrom, J., Janes, J., & Patel, A. (2016). "It's somebody else's milk": Unraveling the tension in mothers of preterm infants who provide consent for pasteurized donor human milk. *Journal of Human Lactation*, *32*(1), 95–102.

Fenton, T. R., & Kim, J. H. (2013). A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics*, *20*(13), Article 59. https://doi.org/10.1186/1471-2431-13-59

Herrmann, K., & Carroll, K. (2014). An exclusively human milk diet reduces necrotizing enterocolitis. *Breastfeeding Medicine*, *9*(4), 184–190.

Higgins, R. D., Jobe, A. H., Koso-Thomas, M., Bancalari, E., Viscardi, R. M., Hartert, T. V., Ryan, R. M., Kallapur, S. G., Steinhorn, R. H., Konduri, G. G., Davis, S. D., Thebaud, B., Clyman, R. I., Collaco, J. M., Martin, C. R., Woods, J. C., Finer, N. N., & Raju, T. N. K. (2018). Bronchopulmonary dysplasia: Executive summary of a workshop. *The Journal of Pediatrics*, *197*(6), 300–308.

Kadıoğlu Şimşek, G., Alyamaç Dizdar, E., Arayıcı, S., Canpolat, F., Sarı, F., Uraş, N., & Oguz, S. (2019). Comparison of the effect of three different fortification methods on growth of very low birth weight infants. *Breastfeeding Medicine*, *14*(1), 63–68. https://doi.org/10.1089/bfm.2018.0093

Kantorowska, A., Wei, J. C., Cohen, R. S., Lawrence, R. A., Gould, J. B., & Lee, H. C. (2016). Impact of donor milk availability on breast milk use and necrotizing enterocolitis rates. *Pediatrics*, *137*(3), 1–8.

Ledo, A., Aguar, M., Núñez-Ramiro, A., Saénz, P., & Vento, M. (2017). Abdominal near-infrared spectroscopy detects low mesenteric perfusion early in preterm infants with hemodynamic significant ductus arteriosus. *Neonatology*, *112*(3), 238–245.

Meier, P. P., Patel, A. L., & Esquerra-Zwiers, A. (2017). Donor human milk update: Evidence, mechanisms and priorities for research and practice. *The Journal of Pediatrics*, *180*(1), 15–21.

Panczuk, J., Unger, S., Francis, J., Bando, N., Kiss, A., & O'Connor, D. (2016). Introduction of bovine-based nutrient fortifier and gastrointestinal inflammation in very low birth weight infants as measured by fecal calprotectin. *Breastfeeding Medicine*, *11*(1), 2–5.

Papile, L., Burstein, J., Burstein, R., & Koffler, H. (1978). Incidence and evolution of subependymal and intraventricular hemorrhage: A study of infants with birth weights less than 1,500 gm. *The Journal of Pediatrics*, *92*(4), 529–534.

Patel, A. L., Engstrom, J. L., Meier, P. P., & Kimura, R. E. (2005). Accuracy of methods for calculating postnatal growth velocity for extremely low birth weight infants. *Pediatrics*, *116*(6), 1466–1473.

Pecoraro, L., Agostoni, C., Pepaj, O., & Pietrobelli, A. (2017). Behind human milk and breastfeeding: Not only food. *International Journal of Food Sciences and Nutrition*, *69*(6), 641–646. https://doi.org/10.1080/09637486.2017.1416459

Radmacher, P. G., & Adamkin, D. H. (2017). Fortification of human milk for preterm infants. *Seminars in Fetal & Neonatal Medicine*, *22*(1), 30–35.

Rosas, R., Sanz, M. P., Fernández-Calle, P., Alcaide, M. J., Montes, M. T., Pastrana, N., Segovia, C., Omeñaca, F., & Sáenz de Pipaón, M. (2016). Experimental study showed that adding fortifier and extra-hydrolysed proteins to preterm infant mothers' milk increased osmolality. *Acta Paediatrica*, *105*(12), e555–e560.

Schanler, R. (2005). Randomized trial of donor human milk versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics*, *116*(2), 400–406.

Stoll, B., Hansen, N., Fanaroff, A., Wright, L., Carlo, W., Ehrenkranz, R., Lemons, J. A., Donovan, E. F., Stark, A. R., Tyson, J. E., Oh, W., Bauer, C. R., Korones, S. B., Shankaran, S., Laptook, A. R., Stevenson, D. K., Papile, L. A., & Poole, W. K. (2002). Late-onset sepsis in very low birth weight neonates: The experience of the NICHD Neonatal Research Network. *Pediatrics*, *110*(2), 285–291.

Su, B. H. (2014). Optimizing nutrition in preterm infants. *Pediatrics and Neonatology*, *55*(1), 5–13.

Underwood, M. A., Gaerlan, S., De Leoz, M. L., Dimapasoc, L., Kalanetra, K. M., Lemay, D. G., German, J. B., Mills, D. A., & Lebrilla, C. B. (2015). Human milk oligosaccharides in premature infants: Absorption, excretion, and influence on the intestinal microbiota. *Pediatric Research*, *78*(6), 670–677.

Vázquez-Román, S., Bustos-Lozano, G., López-Maestro, M., Rodríguez-López, J., Orbea-Gallardo, C., Samaniego-Fernández, M., & Pallás-Alonso, C. (2014). Clinical impact of opening a human milk bank in a neonatal unit. *Anales De Pediatría (English Edition)*, *81*(3), 155–160.

Williams, T., Nair, H., Simpson, J., & Embleton, N. (2016). Use of donor human milk and maternal breastfeeding rates: A systematic review. *Journal of Human Lactation*, *32*(2), 212–220.

World Health Organization. (2018). *Guidelines on optimal feeding of low birth-weight infants in low- and middle-income countries*. http://www.who.int/maternal_child_adolescent

Zozaya, C., Díaz, C., & Saenz de Pipaon, M. (2018). How should we define postnatal growth restriction in preterm infants? *Neonatology*, *114*(2), 177–180.