Nutritional supplementation and growth after hospital discharge in very low birthweight newborns: Randomized controlled trial

Suplementação nutricional e crescimento de recém-nascidos de muito baixo peso após alta hospitalar: Ensaio clínico randomizado

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ABSTRACT
Background Evidence is insufficient to show whether fortification has any effect on growth in preterm infants after discharge. **Objective** to verify whether VLBW preterm infants who are supplemented with multicomponent present greater anthropometric measurements than those not supplemented. **Study Design** Parallel randomized controlled trial. A computer-generated random number table was used to allocate the participants. P**articipants** Preterm infants discharged from the NICU of a University Hospital from northeast, Brazil, weighing less than 1,500 g exclusively breastfed at discharge and followed up until they reached 6 months corrected gestational age. **Intervention** intervention group received Nestlé® PreNan® formula, fractionated in 2 g of powder, mixed with the mother's milk twice a day. Control group was exclusively breastfed. Follow-up was conducted until the infants reached 6 months corrected gestational age (CGA). **Outcomes** Growth of the anthropometrics parameters weight, head circumference (HC) and lenth with 6 months of corrected age. Mixed effects model for longitudinal data was used. Interaction according to sex was detected and ajusted. **Results** Weight gain was significantly higher in the intervention group. This effect was verified only for males ($p = 0.001$). No statistically significant association was observed between the intervention and the head circumference or length ($p = 0.211$; 0.597). The weaning rate at the end of follow-up was similar in both groups. **Conclusions** Breastmilk supplementation may improve the weight gain of very low birthweight preterm infants up to six months corrected gestational age. This effect differed by sex and was considered significant only for males.

Trial Registration REBEC (Brazilian Registry of Clinical Trials - Brazilian Ministry of Health) Nº U1111-1131-8413.

Keywords: Breastfeeding, Preterm, Hospital discharge, Growth, Human milk.

RESUMO

As evidências de fundo são insuficientes para mostrar se a fortificação tem algum efeito sobre o crescimento de bebês prematuros após a alta hospitalar. Objetivo de verificar se os bebês prematuros VLBW suplementados com multicomponentes apresentam medidas antropométricas maiores do que aqueles não suplementados. Desenho do estudo Ensaio Paralelo randomizado controlado. Uma tabela de números aleatórios gerada por computador foi utilizada para alocar os participantes. Participantes Bebês prematuros com alta da UCIN de um Hospital Universitário do nordeste do Brasil, pesando menos de 1.500 g exclusivamente amamentados no momento da alta e acompanhados até atingirem a idade gestacional corrigida de 6 meses. O grupo de intervenção recebeu a fórmula Nestlé® PreNan®, fracionada em 2 g de pó, misturada com o leite materno duas vezes ao dia. O grupo de controle era exclusivamente amamentado. O acompanhamento foi realizado até que os bebês atingissem 6 meses de idade gestacional corrigida (CGA). Resultados Crescimento dos parâmetros antropométricos peso, circunferência da cabeça (HC) e comprimento com 6 meses de idade corrigida. Foi utilizado o modelo de efeitos mistos para dados longitudinais. Foi detectada e ajustada a interação de acordo com o sexo. Resultados O ganho de peso foi significativamente maior no grupo de intervenção. Este efeito foi verificado somente para os homens (p = 0,001). Nenhuma associação estatisticamente significativa foi observada entre a intervenção e a circunferência ou comprimento da cabeça (p = 0,211; 0,597). A taxa de desmame no final do acompanhamento foi semelhante em ambos os grupos. Conclusões A suplementação de leite materno pode melhorar o ganho de peso de bebês prematuros com peso muito baixo até seis meses de idade gestacional corrigida. Este efeito diferiu por sexo e foi considerado significativo apenas para os homens.

Registro de Ensaios REBEC (Registro Brasileiro de Ensaios Clínicos - Ministério da Saúde do Brasil) Nº U1111-1131-8413.

Palavras-chave: Aleitamento materno, Pré-termo, Alta hospitalar, Crescimento, Leite humano.

1 INTRODUCTION

Properly nurturing very low birthweight (VLBW) and extreme preterm infants, is one of the challenges of Neonatology. Most of these newborns have significant deficits in energy, protein, minerals, and other nutrients at the time of hospital discharge. [1,2,3,4,5,6,7.]

Current recommendations for parenteral and enteral nutrition during hospitalization are designed to provide nutrients that approximate the growth rate to that of a normal fetus of the same postconceptional age [8,9]. For this, minimal weight loss should be guaranteed in the first days of life, and weight gain should occur at 14 to 16 g/kg/day after recovering the birthweight[10].

After discharge, there are many challenges to maintaining adequate nutrition and uncertainties about the best nutritional practices [3,11]. Although human milk is the best

nutritional source up to six months of life [12] , there is no consensus in the literature that it meets the nutritional needs of the preterm infants (PTI) after hospital discharge [4,13,14].

In 2010, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition (ESPGHAN) [15] recommended that the breastmilk fed to preterm infants who are discharged from the hospital at a subnormal weight for postconceptional age should be routinely supplemented. The high percentage of early weaning due to prolonged hospitalizations and the unavailability of specific formulas for preterm infants in the post-discharge period in some countries, such as Brazil, increase the chance of nutritional deficit and consequent failure of growth[16].

Some alternative nutritional practices in the post-discharge period have been proposed. Some papers compared the use of enriched formulas and conventional preterm formulas[17]. Others compared preterm enriched formulas and formulas for full-term children[18]. However, only two studies comparing exclusively breastfed infants discharged from the neonatal intensive care unit (NICU) with or without supplementation have been identified [19, 20]. These studies involved 246 children, and concluded that the optimal amount and duration of supplementation is still uncertain[21]. Systematic review involving 1456 infants concluded that feeding preterm with fortified human breast milk is associated with modest increases in in-hospital growth rates. Evidence is insufficient to show whether fortification has any effect on long-term growth or neurodevelopment.

This study aimed to verify whether VLBW preterm infants who are breastfed and receive multicomponent formula supplementation of human milk from discharge up to six months corrected gestational age (CGA) have greater weight gain, length, and head circumference than those without supplementation.

2 METHODS

Randomized clinical trial of parallel groups conducted from December 2010 to February 2014, with infants born weighing less than 1,500 g at less than 37 weeks gestation. Infants were discharged from NICU (University Hospital of the Federal University of Maranhão) in exclusive breastfeeding and were followed-up until they reached 6 months CGA.

Children with conditions that potentially alter fetal or postnatal growth, such as major malformations, hydrocephalus, chromosomal disorders, fetal hydrops, congenital infections, maternal drug abuse, continuous maternal use of corticosteroids, twinning or necrotizing enterocolitis sequelae such as short bowel syndrome, were not included.

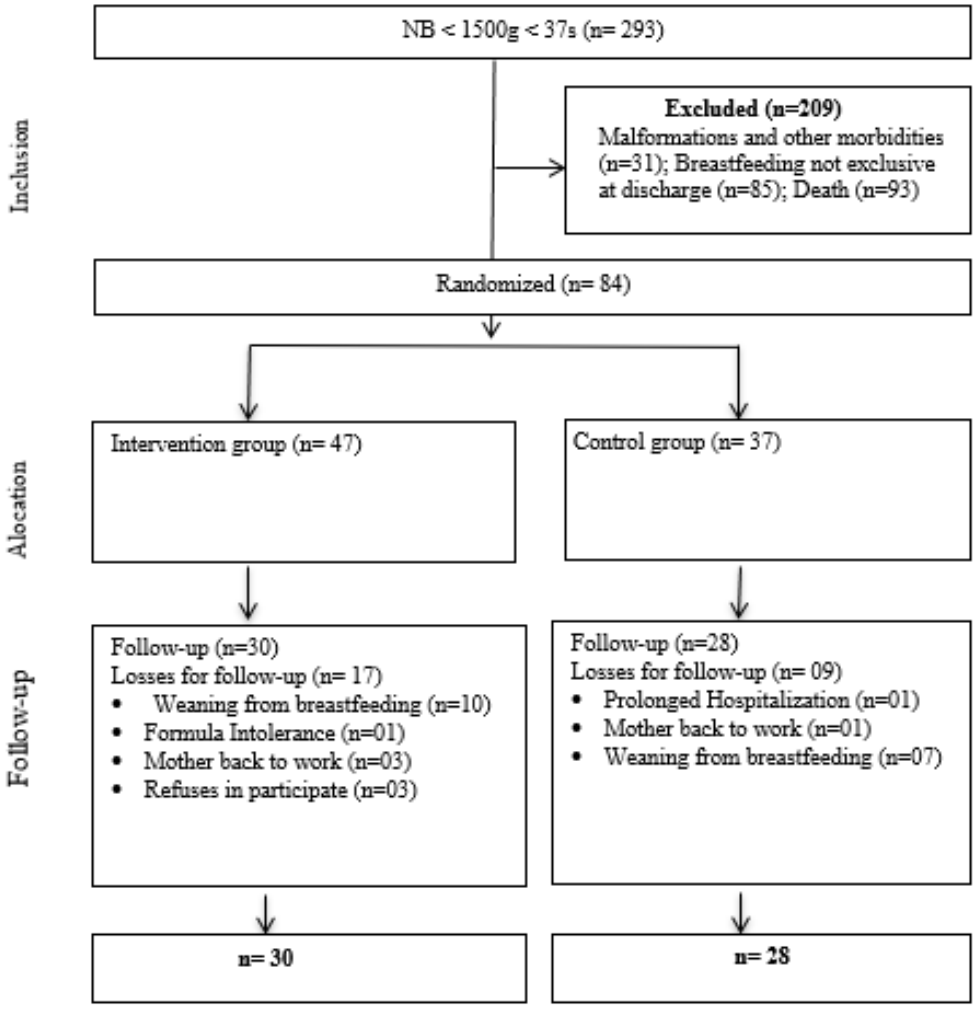
The intervention consisted in an extraction of 10 ml of breastmilk by the mother at home by manual expression and the addition of the supplement. The mother received a packet containing two grams of supplemental powder that she had to mix with the expressed milk and offer this supplemented milk to the child in a 50-ml cup before breastfeeding, twice a day. The procedure was performed daily.

Each day, four grams of powdered formula corresponding to 20 kcal was added to breastmilk. An increase in caloric intake of approximately 140 kcal/kg/day was expected. This supplementation offered an increase of 0.6 g of protein per day. This amount of increase in protein and calories was not adjusted during the intervention period, becoming proportionally smaller as the child gained weight.

An electronic scale with a maximum capacity of 15 kg and an accuracy of 5 g was used to measure body weight. Two professionals measured body length using an acrylic Sanny® stadiometer. The head circumference was measured with a flexible and non-extensible tape, Sanny® brand, graduated in tenths of a centimeter, in the largest occipitofrontal circumference.

During the study period, 293 preterm infants were born in the hospital weighing less than 1500 g. Two hundred nine infants were excluded. Of the 84 children included in the study, 26 did not complete the follow-up. The final study sample consisted of 58 children, 30 in the intervention group and 28 in the control group (Figure 1).

Figure 1 - Randomization Flowchart



Potentially eligible newborns were identified at birth based on NICU admission, weight, and gestacional age (GA). Upon transfer to Intermediate Care Unit, the mother received information on the study objectives and methodology. If the mother consented to participation in the study, she was requested to sign the Informed Consent Form.

During the first clinical appointment, which was conducted 48 to 72 hours after discharge, the babies were randomized into groups if they continued to be exclusively breastfed. PreNan® formula (Nestlé®), fractionated in 2-g packets at a handling pharmacy, was given as a supplement for infants allocated in the intervention group.

Seven to fifteen days after hospital discharge, babies returned to the service for the second appointment with the group of investigators. Information on childcare was provided, and the need to maintain exclusive breastfeeding was reinforced. Thereafter, the children's next appointments were scheduled monthly based on CGA.

A computer-generated random number table was used to allocate the participants. The results were stored in black, sealed envelopes. To create the study and control groups, the lead researcher performed the allocation sequence by opening these envelopes in the presence of the mother.

In this study, mothers and researchers were aware of the allocation to the intervention and control groups. Only the professionals who did the analysis of the results were blind to the allocation. No placebo was used.

2.1 STATISTICAL ANALYSIS

In the first analysis, the characteristics of infants in both groups were described. The variables included weight, gestational age, head circumference, and length at birth; 5-min Apgar score; weight-to-gestational age relationship; illness severity score (SNAP-PE II)[23] at admission; and weight at randomization.

To compare the monthly changes in anthropometric measurements (represented by the z-score of weight, length and head circumference), a mixed effects model for longitudinal data was used. This analysis allows one to describe a temporal trend, taking into account the correlation between successive measures and to estimate the baseline variation and rate of change over time [24].

The covariables included in the model were group (1 = intervention, 0 = control), sex (1 = male, 0 = female), and SGA (1 = yes, 0 = no). To investigate whether the association between group and anthropometric measures differed according to sex, an interaction term was included in the mixed effects model, and its significance was tested. Once this interaction was statistically significant, the analyses were performed considering the total sample separated by sex.

The normality of the variables was tested using the Shapiro-Wilk test. The data were entered in the EpiInfo program, version 3.5 (CDC, Atlanta, GA, USA), and the statistical analysis was performed in STATA 13.

The research complied with Resolution No. 196/96 of the National Health Council and its complements that address the ethics in research carried out with human beings in Brazil. The study was approved by the Ethics in Research Council of the Hospital Universitário da Universidade Federal do Maranhão (Opinion No. 302/10). The study was registered in the REBEC (Brazilian Registry of Clinical Trials) of the Brazilian Ministry of Health under number U1111-1131-8413.

The study sample consisted of 58 children, 30 in the intervention group and 28 in the control group (Figure 1). For a significance level of 95%, detection power of 80, considering an exposed / unexposed ratio of 1, a total sample of 58 individuals was calculated. In each group, the primary outcome was growth over six months, estimated by measuring weight (grams), length (cm), and head circumference (cm). The same evaluator, who was blinded to the allocation group, took these measures at 1, 2, 3, 4, 5 and 6 months CGA.

3 RESULTS

Mothers between 20 and 30 years old corresponded to 65.4% of the sample. Overall, 55.2% of the sample reported a family income between 1 and 3 minimum wage, and 67.3% had 8 to 11 years of education. Fifty-three percent of the women were gainfully employed, and 84.6% were married or lived in consensual union.

The weaning rate at the end of follow-up was 19.1% in the intervention group and 21.8% in the control group (p = 0.999).Children in the intervention and control groups had a similar profile in terms of most perinatal variables (Table 1).

Table 1 - Perinatal characteristics of infants born preterm for intervention and control groups. São Luís, 2010-2014

VARIABLE	**INTERVENTION (30)**	**CONTROL (28)**
	MEAN ± SD	MEAN ± SD
Birthweight (g)	1281.0 ± 196,3	1312,3 ± 171,6
HC at birth (g)	27,7 ± 2,0	27,8 ± 1,3
Birth Length (cm)	38,0 ± 3,4	38,0 ± 2,5
Weight at randomization (g)	1923,8 ± 160,9	1946,7± 132,3
GA at birth (weeks)	31,1 ± 2,3	30,7 ± 2,4
Apgar score 5 min.	8,2 ± 0,9	8,1 ± 1,2
#SNAP-PE II score	11,6 ± 15,8	14,3 ± 10,4
	n (%)	**n (%)**
SGA	13 (43,3)	11 (39,3)
Male sex	12 (40,0)	9 (32,1)

SD = Standard Deviation. SGA = Small for Gestational Age; # SNAP-PE II = Score for Neonatal Acute Physiology with Perinatal Extension-II.

The results of the random mixed effects models adjusted for each anthropometric measure and for the interaction with sex are showed in Table 2. A greater weight gain of supplemented infants compared to non-supplemented infants (p = 0.001).

No statistically significant association was observed between the intervention and head circumference (p = 0.211). However, there was a negative association of head

circumference with SGA (p = 0.008) and male sex (p < 0.001). There was also no interaction between head circumference and the sex/intervention term (Table 2).

There were no statistically significant associations between the intervention and length (Table 2). No clinical complications were detected in any of the groups.

Table 2. Mixed effects linear model for association between intervention and weight, head circumference and length with adjustments for gender, SGA and interaction for sex and intervention. São Luís, 2010-2014.

Weight			
Variables	Coefficient	p-value	95% IC
Intervention	0,234	0,001	0,099 – 0,368
Male gender	0,028	0,796	-0,188 – 0,245
SGA	-0,112	0.077	-0,235 – 0,012
Gender/ Intervention	-0,502	0,001	-0,797 – -0,207
head circumference			
Variables	Coefficient	p-value	95% IC
Intervention	-0,657	0,211	-0,168 – 0,373
Male gender	-0,191	<0,001	-0,289 – -0,092
SGA	-0,082	0.008	-0,142 – -0,022
Gender/ Intervention	0,069	0,391	-0,089 – 0,227
length			
Variables	Coefficient	p-value	95% IC
Intervention	0,058	0.597	-0,157 – 0,272
Male gender	-0,148	0.360	-0,467 – 0,169
SGA	-0,136	0.168	-0,329 – 0,057
Gender/ Intervention	0,211	0.333	-0,217 – 0,639

SGA - Small for Gestational Age.

4 DISCUSSION

In this study, only weight gain was higher in the supplemented group than in the control group. This effect was verified only for males after adjusting for the interaction between the intervention and sex.

Several dietary regimens have been proposed to optimize the growth of VLBW preterm infants after discharge from the NICU. In 2007, Griffin and Cooke [25] published a non-systematic review including several randomized clinical trials comparing the growth of preterm infants fed with difference types of formula in the post-discharge period. They showed a benefit of the use of fortified formula for weight gain.

Evidence for the benefits of supplementation for exclusively breastfed infants is less clear. However, it is known that babies fed exclusively with breast milk in the post-discharge period do not reach the same growth rates as babies fed exclusively with formula[26].

The literature is divided about the effect of breastfeeding supplementation on the weight of VLBW infants after hospital discharge. In a meta-analysis updated in 2013,

Young et al.[21] found no consistent evidence that feeding preterm infants with fortified breastmilk for up to three or four months post-discharge affects growth parameters at the end of the first two years of life.

A systematic review of the literature on PTI nutrition (2016), showed that breastmilk supplementation and enriched diets after discharge have little effect on neurodevelopment, do not have negative effects, and improve growth, especially in boys[5].

In the meta-analysis conducted by Young et al., only two randomized controlled trials were considered eligible. O'Connor et al. in 2008[19], studied children born at 750 to 1800 grams who were fed an in-hospital human milk fortifier (Similac Human Milk Fortifier-Abbott Nutrition, Montreal, Quebec, Canada). At the twelve-week post-discharge follow-up, the children in the intervention subgroup of less than 1250 g birth weight were taller. There was no significant difference in weight.

Zachariassen et al. in 2011, conducted another randomized controlled trial. All children were exclusively breastfeeding and received supplementation with breastmilk fortifier (Enfamil Human Milk Fortifier, Mead Johnson Nutritional, Evansville, IN) until they reached four months CGA. They reported no statistically significant difference in weight, height, or head circumference between the study groups at 2, 4, 6, or 12 months CGA[20].

Brown et al., in 2021, corroborated these results showing that there was insufficient evidence to clarify whether the fortification had any long-term effects on the growth or neurodevelopment of these children[22].

The cut-off points for weight and GA in the study by Zachariassen et al.[20] were between 535 and 2255 g and 33 weeks or less at birth. O'Connor et al.[19] studied children younger than 33 weeks GA weighing less than 1800 g at birth. We studied children < 37 weeks GA with a birthweight < 1500 g. There is an inversely proportional relationship between birthweight and nutritional difficulties, which may have contributed to the different results of these studies.

In the present study, the intervention initially offered an increase of 14.23% more energy and 9.3% more protein per day. The study by O'Connor et al.[19] offered an increase of 10% more energy and 20% more protein per day to the supplemented group. The study by Zachariassen et al. [20] offered approximately 6.5% more energy and 20% more protein per day added to 20-50 ml of breastmilk to the supplemented group.

The use of different supplements, with a higher percentage of energy than that used in the current research, may be a possible explanation for the divergent results among

the three studies. In addition, this study used preterm formula as a fortifier, whereas other studies used human milk fortifier. It is possible that some factor related to the digestibility of different supplements is partly responsible for the different results. Thus, different methodologies may be involved in explaining the different results between this study and the other cited studies.

In the current study, larger weight gains in supplemented children occurred only in males. Different patterns of growth among male and female children are well documented in the literature. During different periods of life, the growth process differs in intensity, speed, and body location between the sexes[27]. It is possible that sex-specific differences in metabolism explain this finding.

The hypothesis that children in the intervention group gained more weight than those in the control group because they were better cared for during follow-up was unlikely, because contact between the mothers and the team was similar in both groups.

The results of the present study indicate that fortification of breastmilk with a multicomponent supplement up to six months CGA may improve the weight gain of preterm VLBW infants after discharge from the neonatal unit compared to those not supplemented. This effect varied according to the sex of the child and was only significant for male children. In addition, this intervention was safe from a clinical point of view and did not interfere with the weaning rate.

The use of formula for preterm infants as a human milk fortifier at home seems to be a good option because such formula is cheaper, easier to obtain and less complicated to handle than hospital fortifiers, especially in low income countries such as Brazil.

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