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ORIGINAL ARTICLE

Nutrition in extremely low birth weight infants: impact on bronchopulmonary dysplasia

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ABSTRACT

BACKGROUND: Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects premature infants with multifactorial etiology. Some authors have considered malnutrition to be a major factor promoting BDP. The aim of our study was to examine the contribution of enteral and parenteral nutritional intake in the first 14 days of life to the development of bronchopulmonary dysplasia in a sample of preterm infants.

METHODS: A prospective cohort study was conducted on all preterm infants born between 1 January 2008 and 31 December 2013. The nutritional parameters compiled included the cumulative amount of fluids, calories, proteins, carbohydrates and lipids consumed. Statistical analysis of the data consisted of a descriptive analysis, Mann-Whitney pairwise comparison test and logistic regression.

RESULTS: The total caloric intake in the infants studied was significantly lower in patients with subsequent bronchopulmonary dysplasia (76.1 kCal/kg, 95% CI: 71.2-81.1 *vs*. 91.1 kCal/kg, 95% CI: 87.5-94.8). The intake of carbohydrate and fat was significantly lower in the patients with BPD (11.6 g/kg, 95% CI: 11.1-12.0 *vs*. 12.6 g/kg, 95% CI: 12.1-13; and 2.5 g/kg, 95% CI: 2.3-2.7 *vs*. 3.4 g/kg, 95% CI: 2.9-3.9, respectively).

CONCLUSIONS: Our study shows that infants who develop bronchopulmonary dysplasia receive a lower enteral intake of calories and total lipids during the first 14 days of life.

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Key words: Bronchopulmonary dysplasia - Infant nutrition disorders - Energy intake - Newborn infant - Extremely low birth weight infant.

Bronchopulmonary dysplasia (BPD) is a chronic lung disease that affects premature infants and is an important cause of morbidity and mortality in this population. Compared with term infants, very low birth weight (VLBW) infants have a higher proportion of extracellular water, which decreases naturally during the first days of life with increased lung fluid content and decreased lung compliance, requiring greater concentrations of inspired oxygen, which might provoke BPD.[1] Furthermore, some authors have observed that most extremely low birth weight (ELBW) infants, *i.e*. those weighing less than 1000 g at birth, with BPD present severe extrauterine growth restriction, increased water intake [2] and reduced caloric intake.[3, 4]

The nutritional intake or concomitant infections, play an important role in the development of this "new bronchopulmonary dysplasia". Like some authors, we believe that children with bronchopulmonary dysplasia receive a lower intake of calories than do infants without bronchopulmonary dysplasia. Our results show that children who develop bronchopulmonary dysplasia achieve full en-

teral nutrition later than do infants without bronchopulmonary dysplasia. Our study supports the view of the importance of parenteral fluid inputs during the first weeks of life on bronchopulmonary dysplasia. Like other authors reported a decrease in the severity of bronchopulmonary dysplasia following the introduction of nutritional strategies that include an increased caloric intake from the first day of life, our study shows that infants who develop bronchopulmonary dysplasia receive a lower enteral intake of calories and lipids during the first 14 days of life.

In recent decades, the use of antenatal steroids and pulmonary surfactant has reduced the incidence of BPD, the severity of which is graded in accordance with the need for supplemental oxygen or positive airway pressure at 36 weeks' corrected gestational age.[5] The increased survival of VLBW and ELBW infants has changed the framework of BPD, from its traditional association with oxygen therapy toward the consideration of a new condition, which some authors [6, 7] have termed "new BPD", more closely related to lung immaturity in extreme preterm infants, impaired alveolarization, and fibroproliferation. Other factors too, such as nutritional intake or concomitant infections, play an important role in the development of this new BPD. As well as the prenatal inflammation that is facilitated by some infections,[7, 8] some authors have considered malnutrition to be a major factor promoting BDP.[9]

In experimental animal models caloric restriction has been shown to reduce the number of alveoli and to decrease the effective alveolar surface area,[10] which leads us to believe that in the preterm infant poor nutrition may contribute to the development of BPD.[11]

The aim of our study was to examine the association of enteral and parenteral nutritional intake in the first 14 days of life to the development of BPD in a sample of VLBW preterm infants.

Materials and methods

A prospective cohort study was conducted at the Neonatal Intensive Care Unit (NICU) of our Hospital. The study was approved by the hospital ethics committee and informed consent for the use of their data was obtained from the patients' parent or guardian.

Data collection

Starting from 1 January 2008 data from all infants was gathered and included in the NEOSOFT database. On 31 December 2013 we completed a rough cut of our analysis, after 6 years of follow-up.

We included all infants weighing less than 1500 g at birth. Infants who died in the first 28 days of life and patients transferred to other hospitals were excluded from the analysis, as it is not be possible to establish the degree of BPD.

The following demographic variables were obtained from the patients included in the study: birth weight, gestational age, mode of delivery, presence of chorioamnionitis, Apgar score at 5 minutes and complete lung maturation with antepartum steroid treatment.

The nutritional parameters compiled included the cumulative amount of fluids, calories, proteins, carbohydrates and lipids consumed in the first 14 days of life. Body weight was recorded at birth and on days 7 and 14 of postnatal life. The Z score was calculated at each of these times, in accordance with the Fenton growth charts,[12] and the difference in Z score was calculated at times t_7 and t_{14} and at birth (t_0). The days elapsed until the establishment of full enteral feeding, and the days of parenteral feeding, were recorded. Other data registered included the days of oxygen therapy, the days of mechanical ventilation and of continuous positive airway pressure (CPAP), and the comorbidity associated with each group, such as retinopathy of prematurity (ROP), sepsis, patent ductus arteriosus and necrotizing enterocolitis (NEC).

Definition of bronchopulmonary dysplasia

According to the NIHCD definition [13] and to Jobe and Bancalari,[5] BPD is defined for oxygen requirement >21% at 28 days of life and/or oxygen requirement >21% or positive

airway pressure at 36 weeks' corrected gestational age, establishing the degree of severity as mild, moderate, severe BPD.

Definition of retinopathy of prematurity

The diagnosis and staging of ROP were based on retinal examination before discharge with severe ROP defined as stages 3 to 5.[14] In ROP, the presence of at least one of the following findings meant the eye was classified as having an unfavorable outcome: a retinal fold involving the macula; a retinal detachment involving zone I of the posterior pole; retrolental tissue, or "mass".[15] The unfavorable structural outcome is taken from the CRYO-ROP and only include lesions defined in order to compare our results [16] with other studies.

Definition of intraventricular hemorrhage and periventricular leukomalacia

The diagnosis of intraventricular hemorrhage (IVH) was based on Papile classification.[17] In all newborns we performed a transfontanellar ultrasound on the third day of life and every week. Periventricular leukomalacia (PVL) is characterized by focal areas of white matter necrosis adjacent to the external angles of the lateral ventricles. We distinguish between echogenic and cystic periventricular leukomalacia. In all children with ultrasound diagnosis of intraventricular hemorrhage or periventricular leukomalacia magnetic resonance imaging of the brain was performed.

Enteral nutrition

The nutritional protocol applied in our NICU recommended that enteral feeding should begin when hemodynamic stability was established in the newborn, with volumes of 0.5 mL/h of breast milk or preterm formula for those weighing less than 750 g and 1 mL/h for those weighing more, with gradual subsequent increases (not quantified) according to tolerance. Fresh or frozen milk was used on most occasions. When this was not possible preterm formula was used. During this period no milk bank was used, in the absence thereof. In this period the use of probiotics was unusual. As a result, full enteral feeding was normally achieved after two weeks of life and fortified human milk was rarely used before this age. In January 2013, this protocol was revised in accordance with recommendations that VLBW infants should receive a higher caloric and protein intake,[18, 19] the main changes include more early onset of inputs of parenteral fat, use of parenteral nutrition on the first day, use of probiotics since the start of enteral nutrition.

Parenteral nutrition

Similarly, the protocol for parenteral nutrition remained unchanged until January 2013, when it was updated to incorporate the latest recommendations.[20, 21] The new approach consisted of an earlier start to protein intake (from the first day of life) and the supply of lipids from the second day of life, with daily increments to 3 g/kg/day. The former protocol for parenteral nutrition had recommended starting, on the first day of life, with volumes of 70-80 mL/kg. Parenteral nutrition was not considered on the first day of life, and protein intake rarely exceeded 3.5 g/kg/day; lipids were not supplied until approximately day 4 or 5 of life, irrespective of possible catchup growth requirements.

In most cases, enteral nutrition was supplemented with parenteral nutrition. The daily requirements of liquids, proteins and lipids were calculated daily. In all cases, the aim was that during the first two weeks of life the following minimum nutritional requirements to ensure growth should be met, according to standard recommendations.[22, 23]

Statistical analysis

Statistical analysis of the data consisted of a descriptive analysis and the Shapiro-Wilk test for normality. When it was found that most of the variables did not follow a normal distribution, a Mann-Whitney pairwise comparison test was performed, together with a multinomial regression analysis taking as the depen-

dent variable the different degrees of BPD (none, mild, moderate, or severe).

The presence of patent ductus arteriosus is one of the variables for which we necessarily have to adjust our models, because it has clinical relevance and delay the withdrawal of ventilatory support associated with BPD. The adjustment variables considered were initially: days of invasive mechanical ventilation, days of CPAP, FiO_2 high, NEC, gestational age, weight, patent ductus arteriosus, antenatal and postnatal steroids and sepsis (if we also include the use of inotropic drugs observed a phenomenon of overfitting, since almost all patients who needed inotropic drugs had sepsis). Finally we adjust the model with the independent variables that can modify the days of oxygen therapy (gestational age, ductus arteriosus, NEC and sepsis). We did not adjust the model with days of oxygen, ventilation with positive pressure to avoid overfitting, being this criteria necessary to define BPD grade.

All reported P values are two-sided and the level of significance was set at 0.05. All analyses were performed using SPSS Statistics v.15.0 (IBM Corp., Chicago, IL, USA).

Results

Perinatal outcomes

From January 2008 to December 2013, 226 VLBW infants were treated in our NICU. Of these, 32 were excluded from analysis due to death in the first two weeks of life. The prevalence of BPD during the period was 45.9%. Table I shows the perinatal data for patients with and without BPD. As was to be expected, the gestational age and weight of the patients who developed BPD was lower (P<0.001), also persistent ductus arteriosus and sepsis is more frequent among patients with BPD (Table II), indicating the need to adjust subsequent comparisons with these variables.

Patterns of nutritional attention

As shown in Table III, in the first two weeks of life a progressive weight loss was recorded, affecting patients with and without BPD. There was a corresponding decrease in the weight Z scores, with no significant differences between

TABLE I.—*Perinatal data for infants with bronchopulmonary dysplasia (BPD) and non-BPD (NBPD).*

	BPD	NBPD
Patients (N.)	89	105
Gestational age (weeks)	27.8±1.9	30.4±1.5 †
Birth weight (grams)	1016±204	1318±239 †
Apgar score at 5 minutes (median)	7.7±2.0	8.8±1.1
Female infants (N.)	36 (40.4%) *	63 (60%)
Small for gestational age (N.)	24 (26.9%)	28 (26.7%)
Maternal age (years)	31.2±6.2	31.2±5.6
Caesarean section (N.)	72 (80.9%)	86 (81.9%)
Completed courses of antenatal steroids (N.)	54 (60.7%)	62 (59.0%)
Surfactant/treatment (N.)	51 (57.3%)	24 (22.8%) †
Chorioamnionitis (N.)	15 (16.9%)	5 (4.8%)

*P<0.05; †P<0.001 *vs*. NBPD.
Data are mean ± standard deviation or number and percentage (in parentheses).

TABLE II.—*Oxygen therapy and morbidity associated with each group.*

	BPD (N.=89)	NBPD (N.=105)
Days of oxygen	60.0±64.6 †	10.7±10.3
Days of mechanical ventilation	12.7±18.0 †	1.2±2.6
Days of CPAP	9.9±8.2 †	3.2±3.6
Ductus arteriosus	26 (29.2%) §	11 (10.5%)
Sepsis	65 (73.0%) †	34 (32.4%)
ROP		
Grade 1	11 (12.4%)	14 (13.3%)
Grade 2	5 (5.6%)	0
Grade 3	21 (23.6%) §	5 (4.7%)
NEC	24 (26.9%) §	12 (11.4%)
IVH		
Grade 1	9 (10.1%)	7 (6.6%)
Grade 2	9 (10.1%) §	2 (1.9%)
Grade 3	8 (8.9%) §	1 (0.95%)
Grade 4	2 (2.2%)	0

§P<0.01; †P<0.001 *vs*. NBPD.
BPD: bronchopulmonary dysplasia; NBPD: no bronchopulmonary dysplasia.

TABLE III.—*Z score for weight at days 0, 7 and 14 for VLBW infants with BPD and NBPD.*

	BPD (mean, 95% CI)	NBPD (mean, 95% CI%)	P
Zw t_0	-0.46 (-0.26 to -0.65)	-0.35 (-0.15 to -0.55)	0.09
Zw t_7	-1.13 (-0.95 to -1.30)	-0.96 (-0.78 to -1.13)	0.22
Zw t_{14}	-1.25 (-1.08 to -1.41)	-1.04 (-0.87 to -1.20)	0.07

NS: not significant; BPD: bronchopulmonary dysplasia; NBPD: no bronchopulmonary dysplasia.

TABLE IV.—*Total nutrient intake mean of the first two weeks of life.*

	BPD (mean, 95% CI)	NBPD (mean, 95% CI)
Days to full enteral nutrition	25.2 (21.4-29.0)	11.5 (9.99-13.0) †
Days of parenteral nutrition	23.1 (20.0-26.3)	9.1 (7.8-10.4) †
Enteral fluids (mL/kg)	26.1 (20.2-32.1)	55.3 (44.6-66.1) †
Parenteral fluids (mL/kg)	109.5 (102-117)	80.0 (69-91) †
Total fluids (mL/kg)	136.3 (132-140)	135.4 (129-141)
Enteral calories (kCal/kg)	18.1 (13.7-22.4)	41.3 (33.0-50.0) §
Parenteral calories (kCal/kg)	58.1 (53.2-62.9)	49.8 (42.3-57.4)
Total calories (kCal/kg)	76.1 (71.2-81.1)	91.1 (87.5-94.8) †
Enteral proteins (g/kg)	0.5 (0.33-0.63)	0.95 (0.69-1.20) §
Parenteral proteins (g/kg)	2.2 (2.0-2.4)	1.7 (1.4-2.0) *
Total proteins (g/kg)	2.7 (2.5-2.9)	2.7 (2.5-2.9)
Enteral carbohydrates (g/kg)	2.1 (1.6-2.5)	4.3 (3.4-5.2) †
Parenteral carbohydrates (g/kg)	9.6 (9.0-10.1)	8.2 (7.9-9.2)
Total carbohydrates (g/kg)	11.6 (11.1-12.0)	12.6 (12.1-13) §
Enteral lipids (g/kg)	0.95 (0.72-1.17)	2.2 (1.6-2.8) §
Parenteral lipids (g/kg)	1.6 (1.4-1.8)	1.2 (0.97-1.5)
Total lipids (g/kg)	2.5 (2.3-2.7)	3.4 (2.9-3.9) †

*P<0.05; §P<0.01; †P<0.001 BDP *vs*. NBPD. (BPD, bronchopulmonary dysplasia; NBPD, no bronchopulmonary dysplasia).

TABLE V.—*Results of multinomial logistic regression for nutrient intake in the first two weeks of life and mild, moderate and severe BPD (dependent variable).*[7] *Values are shown as adjusted OR for gestational age, patent ductus arteriosus, NEC and sepsis.*

	OR (95% CI) Mild BPD	OR (95% CI) Moderate BPD	OR (95% CI) Severe BPD
Days to full enteral nutrition	1.080 (1.024-1.138) §	1.096 (1.036-1.160) §	1.172 (1.092-1.258) †
Days of parenteral nutrition	1.112 (1.050-1.176) †	1.122 (1.055-1.193) †	1.240 (1.135-1.354) †
Enteral fluids (mL/kg)	0.998 (0.996-1.000)	0.998 (0.995-1.000)	0.994 (0.989-0.999) *
Parenteral fluids (mL/kg)	1.002 (1.000-1.004)	1.002 (1.000-1.004)	1.006 (1.001-1.010) §
Total fluids (mL/kg)	1.000 (0.996-1.003)	1.000 (0.996-1.003)	1.007 (0.999-1.014)
Enteral calories (kCal/kg)	0.998 (0.995-1.000)	0.996 (0.993-1.000) *	0.990 (0.987-1.000)
Parenteral calories (kCal/kg)	1.001 (0.999-1.004)	0.999 (0.996-1.002)	1.002 (0.997-1.006)
Total calories (kCal/kg)	0.994 (0.988-1.000) *	0.989 (0.983-0.995) §	0.991 (0.984-0.998) §
Enteral protein (g/kg)	0.960 (0.874-1.154)	0.961 (0.868-1.065)	0.890 (0.718-1.104)
Parenteral protein (g/kg)	1.024 (0.956-1.096)	0.994 (0.927-1.066)	1.088 (0.957-1.238)
Total protein (g/kg)	0.999 (0.920-1.084)	0.963 (0.884-1.049)	1.027 (0.905-1.164)
Enteral carbohydrates (g/kg)	0.976 (0.948-1.004)	0.974 (0.943-1.005)	0.950 (0.896-1.008)
Parenteral carbohydrates (g/kg)	1.012 (0.990-1.035)	1.002 (0.980-1.025)	1.007 (0.973-1.042)
Total carbohydrates (g/kg)	0.977 (0.935-1.021)	0.946 (0.902-0.992) *	0.944 (0.892-0.998) *
Enteral lipids (g/kg)	0.949 (0.895-1.007)	0.947 (0.888-1.010)	0.892 (0.784-1.014)
Parenteral lipids (g/kg)	1.049 (0.970-1.133)	0.984 (0.910-1.064)	1.055 (0.937-1.187)
Total lipids (g/kg)	0.901 (0.808-1.005)	0.826 (0.732-0.931) §	0.845 (0.734-0.974) *

*P<0.05; §P<0.01; †P<0.001 BDP *vs*. NBPD.

the groups. Table IV shows that the infants with BPD achieved full enteral feeding at 25 days, on average (SD=16.0), while infants without BPD achieved full enteral feeding at 11 days (SD=7.5). The preterm infants who subsequently developed BPD took longer to achieve full enteral feeding, and the duration of parenteral nutrition was more prolonged than for infants without BPD. These differences are also observed after adjusting for gestational age, presence of sepsis and ductus arteriosus (Table V). The difference in total fluid intake in patients with and without subsequent BPD did not differ significantly (1896±247 *vs*. 1908±200) although parenteral fluids provided in infants developing BPD are significantly higher.

Our results show that during their first two weeks of life the patients with subsequent

BPD received a lower caloric intake than that recommended.[22, 23] These differences arose as a result of a lower enteral calorie intake, since the calories provided parenterally did not vary significantly between the groups. As shown in Table V after adjusting for gestational age, sepsis and patent ductus arteriosus note that the total caloric intake has a protective effect on the development of BPD.

Table V shows that, overall, the level of calories administered parenterally was not protective effect on BPD.

The total protein intake did not differ significantly between groups; the average intake in BPD group was 2.7 g/kg (95% CI: 2.5-2.9), lower than recommended.[22, 23] However, enteral protein intake was significantly lower in the patients who developed BPD. Multinomial logistic regression analysis indicated that total administered proteins were not associated with BPD (Table V).

Finally, the intake of carbohydrate and fat was significantly lower in the patients with BPD, mainly due to the difference in the quantity of carbohydrate and fat provided enterally. Multinomial logistic regression analysis indicated that the quantity of parenterally administered lipids was not associated with BPD. However, the amount of total lipids provided in the first 14 days of life was associated with a protective effect against the development of BPD (Table V).

Clinical results and morbidity

Table II shows the oxygen treatment received by each group, together with other aspects of neonatal morbidity. As was to be expected, the children who developed BPD received oxygen for more days and mechanical ventilation and CPAP for longer. In the group with BPD, retinopathy of prematurity (ROP) was observed more frequently (48.2% *vs.* 21.1%). With respect to NEC, significant difference was observed between the children with and without BPD. After adjustment for clinical variables most relevant risk of NEC according to the day of initiation of enteral nutrition is OR=1.29 (95% CI: 1.03-1.61). The risk of NEC by the number of days when we get a complete enteral nutrition is OR=1.08 (95% CI: 1.04-1.22). The frequency of sepsis and patent ductus arteriosus is significantly greater in patients with BPD.

Discussion

This study examines the hypothesis that children who develop BPD receive a lower intake of calories than do children without BPD. Some authors [11, 24] have reported a decreasing prevalence of BPD in recent years, coinciding with improved techniques for volume guaranteed ventilation and a more rational use of oxygen therapy [25, 26] together with increased nutritional inputs of protein and calories, as recommended by the ESPGHAN.[21] The results of our study support the hypothesis that children with BPD receive a lower intake of calories than do infants without BPD. Moreover, the risk of developing BPD increases when caloric intake is reduced during the first 14 days of life in VLBW infants.

Furthermore, our results show that children who develop BPD achieve full enteral nutrition later than do infants without BPD. Possibly it is these children, who present the most severe clinical deterioration, for whom the introduction of enteral nutrition appears most challenging, hence the delay in their reaching full enteral nutrition.

Other comorbidities associated with BPD, such as sepsis, NEC or ductus arteriosus were observed more frequently in patients who develop BPD. To evaluate the effect due to nutrition, we propose a regression analysis adjusted for the presence of sepsis, patent ductus arteriosus, NEC and gestational age. Other authors on a large sample,[27] have proposed statistical adjustment with other variables related to disease severity. Some adjustment variable considered as the "use of inotropic drugs" originated overfitting of the regression (all patients with sepsis received inotropic drugs). Moreover ethnicity showed little variability in our sample.

Our study supports the view of the impor-

tance of parenteral fluid inputs during the first weeks of life on BPD. As reported elsewhere,[2, 28] we found that VLBW infants who develop BPD receive significantly higher inputs of parenteral fluid. However, our results are in line with reported by Wemhöner *et al*.,[29] who observed a similar pattern of total fluid inputs among preterm infants with and without BPD. Nevertheless, we did not observe a significantly higher risk of BPD linked with total fluid intake in the first 14 days of life.

In agreement with other authors,[3, 30] we observed a significantly increased risk of BPD linked with lower caloric intake. This finding was not shared, however, by Wemhöner,[29] who studied the energy intake among a larger sample and observed no significant differences in this respect between children with and without BPD. The hypothesis that malnutrition, especially caloric malnutrition, could have an adverse effect on the development of BPD is long standing;[4] the latter authors suggested that protein malnutrition could make the lungs of the premature infant more vulnerable to oxidation, thus fostering the development of the "new BPD", which is characterized primarily by alveolar rarefaction. However, not all the infants in our study with inadequate protein intake developed BPD, and so we believe that as well as the oxygen therapy received, the protein-calorie intake is another factor that should be considered. Theile *et al*.[11] observed a decrease in the severity of BPD following the introduction of nutritional strategies that include an increased caloric intake from the first day of life. These authors suggested that a decrease in extrauterine growth retardation may be associated with the reduced severity of BPD. Protein intake in all infants (with and without BPD) in our sample was lower than the current recommendations of the ESPGHAN [21] for VLBW infants. Although our Hospital is trying to follow the recommendations of the ESPGHAN, is a fact that the final energy intake is generally provided below ideal. We think that one factor that may influence the delay of enteral nutrition is the fear of NEC. However, according to our own results (unpublished) delayed in enteral nutrition is significantly associated with NEC.

Conclusions

Our study shows that infants who develop BPD receive a lower enteral intake of calories and lipids during the first 14 days of life. This finding appears to be independent of comorbidity that could lengthen the days of oxygen therapy. We observed a protector effect on BPD linked to a intake of daily total calories within the first 14 days of life.

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