Brunnella Alcantara Chagas de Freitas[1,2], Mirene Peloso[1], Guilherme Lobo da Silveira[3], Giana Zarbato Longo[4]

Prevalence and factors associated with bronchopulmonary dysplasia in a referral hospital in Minas Gerais, Brazil

Prevalência e fatores associados à displasia broncopulmonar em hospital de referência para microrregião de Minas Gerais

1. Department of Medicine and Nursing, Universidade Federal de Viçosa - UFV - Viçosa (MG), Brazil.
2. Graduate Program in Nutritional Science, Department of Nutrition and Health, Universidade Federal de Viçosa - UFV - Viçosa (MG), Brazil.
3. Neonatal Intensive Care Unit, Hospital São Sebastião - Viçosa (MG), Brazil.
4. Department of Nutrition and Health, Universidade Federal de Viçosa - UFV - Viçosa (MG), Brazil.

This study was conducted at the Department of Medicine and Nursing and the Department of Nutrition and Health, Universidade Federal de Viçosa - UFV - Viçosa (MG), Brazil.

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Corresponding author:
Brunnella Alcantara Chagas de Freitas
Departamento de Medicina e Enfermagem da Universidade Federal de Viçosa
Avenida P. H. Rolfs s/n - Campus Universitário
Zip Code: 36571-000 - Viçosa (MG), Brazil
E-mail: brupediatria@gmail.com

ABSTRACT

Objective: The aim of the present study was to evaluate the prevalence and factors associated with bronchopulmonary dysplasia at a neonatal intensive care unit.

Methods: The study was a cross-sectional study that used secondary data from premature infants who were born with less than 32 weeks of gestational age and were admitted to a neonatal intensive care unit. Chi-square, Mann-Whitney and multivariate tests were used. Significance was set at $p<0.05$.

Results: A total of 88 premature infants were included in the study. Bronchopulmonary dysplasia occurred in 27.3% of the infants and was related to having a gestational age below 28 weeks (OR: 4.80; 95% CI: 1.50-15.34; p=0.008) and a patent ductus arteriosus (OR: 3.44; 95% CI: 1.10-10.76; p=0.034). The group with bronchopulmonary dysplasia used mechanical ventilation for a longer duration, with a median of 24.5 days ($p<0.0001$). At discharge, the corrected and chronological ages were higher in the group with bronchopulmonary dysplasia ($p<0.0001$), with respective medians of 38.4 weeks and 70.5 days.

Conclusions: In tthis study, the prevalence of bronchopulmonary dysplasia was high; the high prevalence was related to extreme prematurity, patent ductus arteriosus, a longer period under mechanical ventilation and prolonged hospitalization. The increased survival of infants with low gestational age makes this disorder a public health issue.

Keywords: Bronchopulmonary dysplasia; Infant, premature; Infant, low birth weight; Infant, premature, diseases

INTRODUCTION

Perinatal medicine and improvements in neonatal intensive care have led to increased survival of premature infants with very low birth weights. This benefit is countered by the higher incidence of bronchopulmonary dysplasia (BPD), which has become a feared complication in premature infants.[1]

BPD is a chronic pulmonary disease that affects premature infants and contributes to their morbidity and mortality. Despite substantial changes in incidence, risk factors and severity after the introduction of new therapies and mechanical ventilation (MV) techniques, BPD remains common. Its pathogenesis is multifactorial and includes immaturity, oxygen toxicity, infection, patent ductus arteriosus (PDA) and poor postnatal nutrition.[2-8]

According to the population under study, the neonatal care and the diagnostic criteria used, the prevalence of BPD varies from 20 to 40%.[9-11] Knowledge of factors that are associated with BPD development contributes to its prevention; BPD often results in prolonged hospitalization, which has consequences for the

premature infants, their families and society.[12]

The present study assessed the prevalence and factors associated with BPD in premature infants in the Neonatal Intensive Care Unit (NICU) at Hospital São Sebastião in Viçosa (MG), Brazil.

METHODS

Study characteristics

The study was a cross-sectional study that used secondary data from premature infants who were admitted to the NICU at Hospital São Sebastião in the period of January 1, 2008 to December 31, 2010.

The study included premature infants who were born with less than 32 weeks of gestation. Because of the loss of monitoring data, infants who died or were transferred to another hospital before 36 weeks of corrected age were excluded from the study.

The study was approved by the Human Research Ethics Committee at the Universidade Federal de Viçosa (number 063/2011) and informed consent was waived.

Variables analyzed

The variable "outcome, BPD" was categorized as "yes" or "no" and was defined as oxygen-therapy dependence at 36 weeks of corrected age, even in cases that were associated with pneumonia, meconium aspiration, gastrointestinal abnormalities and heart disease.[13,14]

The following explanatory variables were analyzed:

- Maternal characteristics (qualitative): maternal age (less than 20 years, 20 to 34 years and more than 34 years); prenatal care (yes, no); use of antenatal corticosteroid (at least one dose - yes, no); multiple births (yes, no); maternal hypertensive syndrome and termination of labor (cesarean);

- Premature infant characteristics (qualitative): newborn origin (born at another hospital – yes, no); gender; Apgar < 7 at the 5th minute; Clinical Risk Index for Babies (CRIB) ≥ 10;[15] gestational age below 28 weeks; small for gestational age (SGA - weight below the 10th percentile of Lubchenco curves); infant respiratory distress syndrome (IRDS); PDA; late sepsis and the use of two or more doses of surfactant (based on clinical, radiological and/or blood gas parameters). The CRIB score was adopted as a measure of the severity at admission, which is indicated for premature infants with an age below 32 weeks; the CRIB is a simple method that is easy to apply because it is based on record data that are routinely monitored in the first 12 hours after birth;[16]

- Premature infant characteristics (quantitative): time under MV (according to the actual routine, based on clinical, radiological and/or blood gas criteria); total period of oxygen therapy; weight at birth; gestational age at birth (defined by the best estimate between the ultrasonography before 20 weeks, the last menstrual period and the clinical examination); age at onset of enteral feeding; age at onset of parenteral nutrition (PN); age at onset of full diet (150 mL/kg/day);[17-20] age when birth weight was recovered; weight at discharge and corrected and chronological age at discharge.

Statistical analysis

The sample size was calculated using the Stat Calc from Epi Info (version 7.0) with a sample power of 80% plus a 95% confidence interval (95% CI): 84 patients were required.

The relative frequencies, medians and maximum and minimum values were obtained. For the qualitative analysis, a Pearson's chi-squared test or a Fisher's exact test was used, and for quantitative analysis, a Mann-Whitney test was used. A $p<0.05$ was considered significant. A backward LR stepwise multiple regression was applied to explanatory variables that displayed $p<0.20$, which related them to the variable "outcome, BPD (yes or no)". The software Statistical Package for the Social Sciences (SPSS, version 17.0) was used for the analyses.

RESULTS

In the period of study, 502 patients were admitted to the NICU (47.4% of the total population since the unit was opened). Of those, 336 were premature infants (66.9%), and records were found for 293 of the infants. A total of 43.3% (n=127) of the infants were younger than 32 gestational weeks, from whom 24,4% (n=31) died before reaching 36 corrected weeks of age. From those 96 premature infants, eight were excluded from the study because of a loss of monitoring data (they were transferred to another hospital before 36 weeks of corrected age). Thus, after applying the inclusion and exclusion criteria, the final sample had 88 patients.

BPD occurred in 27.3% of the population studied (n=24). Maternal and premature infant characteristics and their association with BPD development were evaluated.

The maternal variables "age", "antenatal corticosteroid use", "at least one prenatal appointment", "twinning", "hypertensive syndrome" and "cesarean delivery" did not differ between the groups with and without BPD (Table 1).

Regarding the premature infant characteristics, the group with BPD was related to a gestational age below 28 weeks ($p<0.0001$), the occurrence of IRDS ($p=0.027$), PDA ($p=0.001$) and late sepsis ($p=0.025$) (Table 2).

The medians for gestational age were lower in the BPD group than in the group without BPD (28.0 and 30.1

Table 1 - Maternal characteristics according to bronchopulmonary dysplasia development

	Bronchopulmonary dysplasia		
Variables	**Yes (N=24)**	**No (N=64)**	**p value**
Mother's age			0.874*
< 20 years	5 (29.4)	12 (70.6)	
20-34 years	12 (26.1)	34 (73.9)	
≥ 35 years	4 (33.3)	8 (66.7)	
Prenatal care	7 (30.4)	16 (69.6)	0.638**
Antenatal corticosteroid	7 (26.9)	19 (73.1)	0.814*
Multiple births	3 (25.0)	9 (75.0)	1.000**
Maternal diseases			
Hypertensive syndrome	4 (18.2)	18 (81.8)	0.381*
Maternal infections	3 (18.8)	13 (81.3)	0.747**
Cesarean delivery	13 (27.7)	34 (72.3)	0.890*

The percentages refer to the total number of valid answers, and absent data were not considered. Significance was set at p<0.05. Data are expressed as percentages. * p value according to Pearson's chi-squared test; ** p value according to Fisher's exact test.

Table 2 - Premature newborn characteristics according to bronchopulmonary dysplasia development

	Bronchopulmonary dysplasia		
Variables	**Yes (N=24)**	**No (N=64)**	**p value**
NI from another hospital	3 (17.6)	14 (82.4)	0.381**
Male gender	16 (30.8)	36 (69.2)	0.376*
Apgar 5th minute < 7	3 (30.0)	7 (70.0)	1.000**
CRIB ≥ 10	4 (66.7)	2 (33.3)	0.056**
GA < 28 weeks	12 (60.0)	8 (40.0)	<0.0001*
SGA	2 (40.0)	3 (60.0)	0.611**
IRDS	22 (33.3)	44 (66.7)	0.027*
PDA	12 (54.5)	10 (45.5)	0.001*
Late Sepsis	15 (39.5)	23 (60.5)	0.025*
Surfactant ≥ 2 doses	6 (54.5)	5 (45.5)	0.302**
BW (g)	1,049 (720-2,328)	1,356 (610-1,890)	0.001***
GA (weeks)	28.0 (26.0-31.5)	30.1 (24.0-31.6)	0.002***
Age at onset of enteral feed (days)	3.0 (1.0-8.0)	3.0 (0.5-18.0)	0.759***
Age at onset of PN (days)	3.0 (1.0-15.0)	3.0 (1.0-11.0)	0.991***
Age at full diet (days)****	24.5 (12-56)	20.0 (9.0-50.0)	0.042***
Age at recovered weight (days)	12.0 (7.0-19.0)	11.0 (4.0-99.0)	0.149***

NI - newborn infant; CRIB - Clinical Risk Index for Babies; GA - gestational age; SGA - small for gestational age; IRDS - Infant respiratory distress syndrome; PDA - Patent ductus arteriosus; BW - birth weight; PN - parenteral nutrition. Data are expressed as percentages and medians (minimum – maximum). The calculations considered the total number of valid answers, excluding the absent data. Significance was set at p<0.05. * p value according to Pearson's chi-squared test; ** p value according to Fisher's exact test. *** p value according to Mann-Whitney test; **** 150 mL/kg/day.

weeks, respectively; p=0.001). Similar outcomes were observed with the birth weight medians, which were 1,049 g and 1,356 g, respectively (p=0.002). A delay in the onset of full diet ingestion was evident in the premature infants with BPD (median of 24.5 days; p=0.042).

Backward LR stepwise multiple regression was applied to variables showing p<0.20, which included gestational age below 28 weeks, birth weight, IRDS, PDA, late sepsis, age at onset of full diet, age of recovered weight and a CRIB score ≥ 10. However, confounding factors for a CRIB score ≥ 10, age at onset of full diet and recovered weight led to their removal from the analysis.

The variables related to BPD occurrence that remained in the final model were gestational age below 28 weeks (OR: 4.80; 95% CI: 1.50-15.34; p=0.008) and PDA (OR: 3.44; 95% CI: 1.10-10.76; p=0.034).

There were significant differences for the period under MV and total oxygen therapy (p<0.0001), and there were higher medians for the period under MV and total oxygen therapy in the BPD group, with values of 24.5 days and 61.0 days, respectively (Table 3).

Table 3 - Ventilation assistance and premature newborn characteristics at discharge according to bronchopulmonary dysplasia development

	Bronchopulmonary dysplasia		
Variables	**Yes (N=24)**	**No (N=64)**	**p value**
Mechanical ventilation time (days)	24.5 (2.0-66.0)	3.0 (0.5-48.0)	<0.0001*
Total period of O_2 (days)	61.0 (33.0-90.0)	12.5 (1.0-72.0)	<0.0001*
Discharge weight (g)	2,667 (1,744-3,635)	2,044 (1,490-3,165)	<0.0001*
Discharge CA (weeks)	38.4 (36.0-40.5)	35.5 (32.0-47.1)	<0.0001*
Discharge ChrA (days)	70.5 (43.0-100.0)	40.0 (8.0-119.0)	<0.0001*

MV - mechanical ventilation; O_2 - oxygen; CA - corrected age; ChrA - chronological age. Results are expressed in medians (minimum – maximum). The calculation considered the total number of valid answers, excluding the absent data. * Significance was set at p<0.05. p value according to Mann-Whitney test.

At the moment of NICU discharge, the variables "weight", "corrected age" and "chronological age" were higher in the BPD group (p<0.0001), with medians of 2,667 g, 38.4 weeks and 70.5 days, respectively. The higher corrected and chronological age at discharge justified the higher weights of premature infants with the disease, as gestational age and birth weight were also lower.

DISCUSSION

In the present study, the BPD prevalence of 27.3% was higher than the prevalence in other studies; previous results have varied from 15.3% to 24%.[14,21,22] However, if the analysis included eight patients transferred back to their hometowns without oxygen support (therefore likely having no BDP; these patients were excluded from the sample as were not followed until 36 weeks of corrected gestational age), the prevalence would be lower, at levels comparable to the mentioned studies. Thus, BPD as a complication of prematurity remains a common disease and a major public health problem because there have been increased rates of infant survival at lower gestational ages.[23]

For the maternal variables analyzed, there were no differences between the groups; however, the use of antenatal corticosteroid is known to be protect against BPD.[11] Gestational hypertension also provides some protection, which is likely related to the birth of more mature premature infants.[24,25] Furthermore, a cesarean delivery may be related to induced prematurity when it is necessary to interrupt the pregnancy.[11]

The present study found a higher occurrence of BPD when prematurity was extreme. Although gestational age is an important predictor of BPD,[21,26-28] there are other factors that contribute to BPD, as shown by the association between BPD and IRDS.[11]

The association between PDA and BPD shown in the present study has been corroborated by other authors,[21,29] although it was not observed by Tauzin et al.[30] Even with the clinical and surgical treatment of PDA, Laughon et al.[31] and Kugelman and Durand[29] did not observe a reduction in the occurrence of BPD. Therefore, conservative clinical measures that aim at PDA prevention should be established, such as fluid restriction and adequate ventilation support.[29,32]

This study found an association between longer MV duration and the occurrence of BPD, which has also been found by other authors.[5,12,27,33,34] A reduction in disease incidence has been reported with the decrease in MV duration.[5,33-38] The increased use of nasal continuous positive airway pressure (CPAP) is suggested as a protective ventilation strategy that is an alternative to invasive ventilation, and the practice of early extubation can lead to reduced MV duration. Authors promote the use of CPAP as the primary therapy or after surfactant administration.[34-38] However, there has been limited success of CPAP maintenance without the need for posterior intubation, especially in extremely premature infants.[39]

The risk of BPD development can be substantially reduced by decreasing MV duration.[5,33] However, one must consider that prematurity, either alone or when it is associated with several perinatal complications, can determine the MV duration and the consequent risk of BPD.[4,27,40,41]

This study has not confirmed the association between BPD and the feeding practices and nutritional aspects that were evaluated. However, the authors confirmed that once the disease had developed, the premature infants required longer durations of ventilation support and hospital stays, which also suggests greater nutritional inadequacy.[11,28] In this regard, early nutritional support is important as a preventive measure for BPD,[29] and there should be an emphasis on the adequate supply of enteral feeding, even with supplementation by parenteral nutrition.[6,42]

The present study highlights the longer duration of hospital stays in the group who developed BPD. The inherent risks of prolonged hospitalization result in social and financial costs that have been corroborated by other authors.[11,28,43]

CONCLUSIONS

The present study has several limitations related to cross-sectional and single-center studies, although it contextualizes a period of three years in the assessed unit, which has been in operation for six years. Because of its characteristics, the present study is not a cause and effect study but one of association.

Reducing the incidence of prematurity is the most effective way to alleviate BPD. If premature birth has occurred, we highlight the necessary dissemination of practices that prevent PDA development and the use CPAP as an alternative to invasive ventilation; additionally, early extubation should aim to decrease the duration of MV. Further studies are suggested to encourage the use of CPAP.

RESUMO

Objetivo: Avaliar a prevalência e os fatores associados à displasia broncopulmonar em uma unidade de terapia intensiva neonatal.

Métodos: Estudo transversal de dados secundários de prematuros nascidos com menos de 32 semanas de gestação, admitidos em uma unidade de terapia intensiva neonatal. Utilizaram-se os testes qui-quadrado, Mann-Whitney e a regressão multivariada. Considerou-se p<0,05.

Resultados: Estudaram-se 88 prematuros. A displasia broncopulmonar ocorreu em 27,3% e se associou à idade gestacional inferior a 28 semanas (OR: 4,80; IC95%: 1,50-15,34; p=0,008) e à persistência do canal arterial (OR: 3,44; IC95%: 1,10-10,76; p=0,034). O grupo com displasia broncopulmonar utilizou maior tempo de ventilação mecânica, com mediana de 24,5 dias (p<0,0001). No momento da alta, as idades corrigida e cronológica foram maiores no grupo com displasia broncopulmonar (p<0,0001), com medianas respectivas de 38,4 semanas e 70,5 dias.

Conclusões: A prevalência de displasia broncopulmonar neste estudo foi elevada, associando-se à prematuridade extrema, à persistência do canal arterial, ao maior tempo de ventilação mecânica e ao prolongamento da internação. Essa morbidade constitui problema de saúde pública em razão do aumento da sobrevida dos prematuros de menores idades gestacionais.

Descritores: Displasia broncopulmonar; Prematuro; Recém-nascido de baixo peso; Doenças do prematuro

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