Influence of maternal and neonatal factors on bronchopulmonary dysplasia development

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Summary

Objective: To review epidemiological features of bronchopulmonary dysplasia (BPD) and its relationship with maternal and neonatal conditions in a neonatal unit. **Methods:** Cross-sectional, descriptive and analytical study involving preterm newborns (NBs) with a birth weight lower than 1,500 g and gestational age under 37 weeks. Data was collected through a review of medical records of these newborns admitted to a neonatal unit. **Results:** The study included 323 newborns with a mean birth weight of 1,161 g (± 231 g), gestational age between 24 and 36.5 weeks, with a BPD incidence of 17.6%. Among the NBs developing BPD, the mean of days using invasive mechanical ventilation (IMV), non-invasive ventilation (NIMV), and supplemental oxygen was 17.6, 16.2, and 46.1 days, respectively, with a time significantly longer for those NBs developing BPD ($p < 0.001$). BPD occurred significantly more often in NBs with a patent ductus arteriosus (PDA). **Conclusion:** BPD incidence in this study was similar to that found in the literature. No BPD association with maternal infection and antenatal corticosteroid use was found. NBs receiving exogenous surfactant had a higher BPD incidence because they had lower BW and GA. Concomitant occurrence of PDA and BPD is associated with staying longer on IMV, NIMV and supplemental oxygen.

Keywords: Bronchopulmonary dysplasia; premature newborns; mechanical ventilation; oxygen therapy; risk factors.

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Introduction

When firstly described by Northway in 1967, bronchopulmonary dysplasia (BPD) was only associated with borderline premature infants developing the respiratory distress syndrome (RDS) and using high airway pressures over the mechanical ventilation (MV) and elevated oxygen concentrations[1]. Since then, important information about neonatal care was acquired, but until today BPD remains as one of the major causes of morbidity and mortality in premature infants[2-4]. Mortality of premature infants has been reduced, however BPD incidence keeps elevated, as increasingly premature infants survive and they have a higher risk for developing associated complications[5,6]. In Brazil, according to data obtained in 2001 from the Brazilian Net of Neonatal Research, BPD incidence ranges from 3.3% to 30% for NBs with a birth weight lower than 1,500 g, with a mean of 18.4%; when only those with a birth weight between 500 and 750 g are considered, the estimated incidence rises to around 70 to 85%[7].

BPD pathophysiology is not fully understood yet, but it is a complex process in which there is a synergistic action of several factors on an immature body undergoing various insults and, at the same time, defense mechanisms are not fully developed[4,8-10]. Initial stimulus activating the inflammatory process may be the action of free radicals secondarily to oxygen therapy, barotrauma, volutrauma, infectious agents, and other stimuli eliciting this disease in a still developing lung[11,12]. Prematurity and low birth weight are considered major risk factors for the disease and other factors have been observed recently, among which the patent ductus arteriosus (PDA) could be mentioned[13-15].

This study aims to review maternal and neonatal risk factors related to BPD development, as well as its incidence among very low birth weight newborns admitted to a neonatal unit at Instituto de Medicine Integral Prof. Fernando Figueira (IMIP).

Methods

This was a cross-sectional, retrospective and descriptive study involving the review of medical records in NBs with a very low birth weight admitted to the neonatal intensive care unit at IMIP. This is a tertiary facility whose neonatal unit receives high-risk newborns. The project has been approved by the Ethics and Research Committee in the mentioned hospital. All NBs with gestational age (GA) under 37 weeks and birth weight (BW) lower than 1,500 g were included over the period between June 2006 and December 2007. NBs carrying malformations, those dying within the first hours of life, those who were not on supplemental oxygen during the hospitalization, and those whose required information was missing were excluded. Patent ductus arteriosus was not considered a congenital malformation, but rather a possible cardiocirculatory complication, in which a fetal pattern is maintained.

Based on the study inclusion criteria, a list of all NBs who could participate in the study (GA < 37 weeks and BW < 1,500 g) was requested to the IMIP Epidemiology Center. Data was collected through a survey and retrospective study of medical records, with the following information being extracted: birth weight, gestational age, gender, diagnostic hypotheses type of delivery, Apgar scores in the first and fifth minute, exogenous surfactant use, patent ductus arteriosus (PDA) diagnosed, days on invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV), days on supplemental oxygen and length of stay in the hospital.

Recorded gestational age was obtained via last menstruation date (LMD); PDA was considered after clinical suspicion was confirmed through echocardiography and BPD diagnosis was made in all NBs on supplemental oxygen with an inspired fraction higher than 21% for a period ≥ 28 days under any administration mode (IMV, NIMV or halo), following the 2000 Consensus Conference[16].

The sample calculation used Epi Info 3.5.1 software and was performed aiming to estimate the BPD incidence. The study target population consisted of 375 live-born infants (number of subjects with a weight lower than 1,500 g and GA < 37 weeks, admitted to the neonatal unit between June 2006 and June 2007). Assuming a 5% estimate error and an expected frequency of the event (BPD) of 20%, a sample size of 246 NBs was determined.

In the statistical analysis, Student's *t* test was used to compare variables with a nearly normal distribution and Pearson's chi-squared test was used to verify the existence of an association between categorical variables and the endpoint. In all tests, 5% significance level was adopted.

Results

In this study, 454 eligible NBs were selected. Among them, 131 patients were excluded, 59 of them with malformations, 34 dying within the first six hours of life, 22 were not on supplemental oxygen over hospitalization, and 16 did not have the required information; thus, the sample consisted of 323 NBs.

In the study sample, 48.9% (158/323) of NBs were male. Birth weight ranged from 590 to 1,490 g, with a mean of 1,161 ± 231 g. GA ranged from 24 to 36.5 weeks, with a mean of 29.8 ± 2.4 weeks. C-section frequency was 49.5% (160/323). Apgar score at the first and fifth minute was higher than seven in 43.3% (140/323) and 89.2% (288/323) of the NBs, respectively. Length of stay in the hospital ranged from 2 to 124 days, with a mean of 44.8 ± 26.4 days. Among the study NBs, 96% had an initial diagnosis of RDS, 16.7% of transient tachypnea of the newborn (TTN), and 30.3% of hypoxia.

BPD incidence in the study sample was 17.6%. NBs with 501 to 999 g were observed to have an incidence of 44.7%, and it was 8% for birth weights between 1,000 and 1,499 g when the newborns were analyzed according to the BW. The incidence of BPD can be better represented when the BW is stratified in more detail, as shown in Table 1.

Among NBs developing BPD, the mean of days on IMV, NIMV, and supplemental oxygen was 17.6, 16.2, and 46.1 days, respectively, which is significantly higher than the mean of days on those supportive measures for NBs who did not develop the disease, as shown in Table 2.

BPD occurrence was significantly higher in NBs with a PDA diagnosis compared with those who did not experience this complication, as demonstrated in Table 3.

NBs with PDA and BPD diagnoses concomitantly had means of days on IMV, NIMV, supplemental oxygen and length of stay in the hospital of 18.6, 16.6, 44.8, and 80.2 days, respectively, while in NBs who did not have the association with those complications the findings of 2.3, 5.6, 11.9, and 40.4 days, respectively ($p < 0.001$) were shown.

Table 4 shows the association of NBs using exogenous surfactant with BPD incidence, with NBs on that therapy having higher incidence of the disease. However, NBs on exogenous surfactant were observed to have mean BW and GA significantly lower than those who did not receive the therapy, as described in Table 5.

Regarding the antenatal corticosteroid use and maternal infection occurrence, no association with BPD incidence was observed.

Discussion

Because of the inconsistent definition of BPD, which makes the clinical diagnosis more difficult to establish, a great variability of the disease incidence was found in several neonatal care centers. Among preterm NBs, BPD incidence can range from 4% to 40%, according to a number of studies, being influenced by factors such as: study population characteristics, ventilation strategy and neonatal care routines[5,9,12]. BPD incidence, in the study sample, was 17.6%, representing values lower than those found by Tapia et al.[10] who reported an incidence of 24.4%. In the study by Miguez et al.[17], conducted from 1997 through 2001, a BPD incidence of 12.5% was found.

As BPD has an incidence that is inversely related to the BW, we observed variations within our sample when different weight ranges were considered. When we compared the incidence of BPD in NBs with a BW between 500 g and 750 g with those with a BW between 751 g and 1,000 g, no significant difference was found, but in the lower weight range, only 16 patients were noted, whereas in the range between 751 g and 1,000 g, 78 NBs were found. For NBs in BW range from 1,251 to 1,499 g, BPD was seldomly seen.

Table 1 – Incidence of bronchopulmonary dysplasia according to the birth weight

	BPD		
	Yes	No	Total
PN	n (%)	n (%)	n (%)
500-750 g	7 (43.8)	9 (56.2)	16 (100)
751-1.000 g	33 (42.3)	45 (57.7)	78 (100)
1.001-1.250 g	12(12.6)	83 (87.4)	95 (100)
1.251-1.499 g	5 (3.7)	129 (96.3)	134 (100)
Total	57 (17.6)	266 (82.4)	323 (100)

BPD, bronchopulmonary dysplasia; BW, birth weight.

Table 2 – Distribution of mean of days on ventilatory support among newborns with and without bronchopulmonary dysplasia

	BPD		
	Yes	No	
Variable	X ± SD	X ± SD	p
IMV (days)	17.6 ± 14.2	1.2 ± 3.0	< 0.001
NIMV (days)	16.2 ± 8.9	4.8 ± 4.4	< 0.001
Oxygen (days)	46.1 ± 15.5	9.0 ± 7.0	< 0.001

X, mean; SD, standard deviation; BPD, bronchopulmonary dysplasia; IMV, invasive mechanical ventilation; NIMV, non-invasive mechanical ventilation.
Student's t-test.

Table 3 – Association of newborns having patent ductus arteriosus with the incidence of bronchopulmonary dysplasia

	BPD		
PDA	Yes	No	p
Yes	36 (63.2%)	21 (36.8%)	< 0.001
No	21 (7.9%)	245 (92.1%)	< 0.001
Total	57 (17.6%)	266 (82.4%)	< 0.001

BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus.
Pearson's chi-squared test.

Table 4 – Association between exogenous surfactant use and incidence of bronchopulmonary dysplasia

	BPD			
Surfactant	Yes	No	Total	p
Yes	46 (28.8%)	114 (71.2%)	160	< 0.001
No	11 (6.7%)	152 (93.3%)	163	< 0.001
Total	57 (17.7%)	266 (82.3%)	323	< 0.001

BPD, bronchopulmonary dysplasia.
Pearson's chi-squared test.

Table 5 – Mean birth weight compared with gestational age, according with exogenous surfactant use

	Surfactant use				
	Yes		No		
Variable	n	X ± SD	n	X ± SD	p
BW(g)	160	1,064 ± 232	163	1,256 ± 186	< 0.001
GA (weeks)	160	28.7 ± 2.1	163	30.9 ± 2.1	< 0.001

X, mean; SD, standard deviation; BW, birth weight; GA, gestational age.
Pearson's chi-squared test.

Fanaroff et al.[18] reported an incidence of 23% among preterm NBs with a BW lower than 1,500 g at the National Institute of Child Health and Human Development (NICHD), in the United States, over the period from 1997 to 2002. The analysis of the sample stratified by BW range revealed that for NBs with a birth weight between 501 g and 750 g, the incidence was 57%; for those with a BW between 751 and 1,000 g, 32%; among those with a birth weight between 1,000 and 1,250 g, 14%, and for those between 1,251 and 1,500 g, only 6%.

Development of BPD is directly related to the time on mechanical ventilation and, according to Gonzaga et al.[19], the possibility of a NB with a BW lower than 1,500 g to develop BPD is 11 times higher if it is kept on IMV for up to 14 days, with furtherly increased chances for those ventilated for over 15 days, which shows extubation is an important feature whenever it is possible over the first week of life. In our study, we observed that among NBs developing BPD, the mean of days on both IMV and NIMV was always higher than 15 days, being significantly higher than the mean of days on those supports in NBs without this complication. Protective ventilatory strategies have been associated with a more favorable short- and long-term course in preterm NBs, with lower mortality and lower BPD incidence[19,20]. As yet, there is no consensus on the appropriate ventilatory support management to reduce the time on IMV and BPD incidence. Early use of a non-invasive ventilatory support and maintenance of lower oxygen peripheral saturation levels are known to be associated with a lower risk for developing BPD[20]. Kobaly et al.[21], when comparing their results from the years 2000 and 2003, observed the implementation of new neonatal intensive care practices, such as antenatal corticosteroid, exogenous surfactant administration and appropriate PDA treatment produced better results, reducing the abnormalities found in skull ultrasonography and the mechanical ventilation dependence. Geary et al.[22] found the early use of surfactant, followed by continuous positive airway pressure (nasal CPAP) with early inspired fractions of oxygen lower than 40% in the delivery room associated with early amino acid administration can reduce BPD incidence and severity. Teixeira et al.[23] observed marked association between hyperoxia and BPD, reporting an arterial blood partial pressure of oxygen (PaO_2) higher than 80 mmHg increased 3.42 times the newborns' chance of developing BPD.

Use of exogenous surfactant has been a valuable tool for modification of the classic BPD "new" DBP[24]. Surfactant replacement therapy in newborns with RDS improves lung function, leading to less need for high concentrations of oxygen and high pressures during mechanical ventilation, but is not effective in reducing the incidence of DBP[24,25]. In our study, we found asignificant association between use of exogenous surfactant and development of BPD. This fact can be better understood when analyzed GA and BW of newborns, there is an inverse relationship between these variables and the development of the disease.

Out of the 57 NBs with a PDA diagnosis in our sample, 63.2% developed BPD. PDA is indicated as a major risk factor for BPD development, as it impacts the cardiopulmonary system, with reduced lung compliance, increased pulmonary vascular resistance, often extending the IMV time. However, few studies show an association between this new risk factor and the disease. The association between PDA and BPD was observed to produce a significant increase in time on mechanical ventilatory support, oxygen therapy and length of stay in the hospital, compared with NBs who did not have PDA and BPD concomitantly.

Behring et al.[26] designed a predictive model trying to identify the probability of NBs progressing to BPD at the end of the first week of life and indicated PDA as one out of four more significant variables. For NBs with a gestational age less than 30 weeks, more than 2 days on mechanical ventilation, and over 15% BW loss up to the seventh day of life, PDA could raise the chances of the disease from 76.5% to 93.7%.

Despite the association found between PDA and BPD, Schmidt et al.[27] suggested in their studies that preventive treatment for PDA seems neither to reduce BPD incidence nor demonstrate a cause-effect relationship, that is, the presence of PDA increases the disease risk, but this risk is not changed when the prophylactic closure of a patent ductus arteriosus is performed.

In our study, we have found no association between maternal factors analyzed (antennal corticosteroid use and maternal infection) and BPD development, concurring with Rocha et al.[28], despite their sample is quite vulnerable, as it included NBs with a BW lower than 1,000 g and severe chorioamnionitis. However, although no significant association between maternal infection and BPD could be found, the presence of maternal infections can, according to a number of authors, induce a premature delivery, a major impact factor on BPD development[28,29].

Regarding antenatal corticosteroid use, no association was found with a lower disease incidence, similarly to the findings by Tapia et al. and by the Brazilian Neonatal Research Network in 2004[30]. This research suggests using antenatal corticosteroids promotes higher survival in preterm NBs, with an increased infection risk.

Van Marter et al.[31] studied 193 NBs with a BW lower than 1,500 g with chorioamnionitis, mechanical ventilation, and postnatal sepsis to better understand the interaction between maternal infection and BPD and they observed extended mechanical ventilation and postnatal infection raised BPD risk among surviving premature NBs. Thus, these two factors interact with prenatal infection, further increasing the risk for developing the disease.

Conclusion

The incidence of BPD found in our sample is in line with the values reported in the literature and BW was a major risk factor for developing the disease, as the analysis of BPD incidence per weight range was found to be higher in those NBs with a lower birth weight. A long time on IMV, NIMV and oxygen therapy, as described in the literature, was associated with a higher incidence of the disease and the neonatal factor showing a strong correlation with BPD was PDA. Positive association of exogenous surfactant use and patent ductus arteriosus with BPD development demonstrated neonatal factors were determinant for the disease in the study sample. However, wider and deeper investigation with a higher number of subjects is warranted to elucidate as many associated factors as possible in order to elicit interventions increasingly early which can produce an impact on morbidity and mortality from this disease.

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