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Original article

Impact of changes in perinatal care on bronchopulmonary dysplasia: an overview of the last two decades

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Abstract

Objective: To compare the clinical approach and outcomes of bronchopulmonary dysplasia (BPD) patients in the last two decades (1996-2005 vs 2006-2015) in a neonatal intensive care unit.

Methods: Out of 1,196 admissions of very low birth weight and/or less than 32 weeks of gestational age infants, 96 had BPD and were dichotomized into two groups according to the year of birth (1996-2005 and 2006-2015). Their clinical data were studied and conclusions were drawn about their morbidity and mortality.

Results: There was a decrease in mortality (23.3% vs. 14.4%, $p < 0.001$) and in BPD prevalence (9.7% vs 6.1%, $p = 0.023$); in the delivery room, early nasal continuous positive airways pressure (nCPAP) was used in 41.2% vs 1.6%, $p < 0.001$ and tracheal intubation in 70.6% vs 96.8%, $p < 0.001$. We observed an increase on the duration of non-invasive ventilation (nCPAP, 22.5 vs 45.5 days, $p < 0.001$) and a decrease of invasive ventilation (39.5 vs 20 days, $p = 0.013$) from the first to the second period.

Conclusions: Improvement in perinatal and neonatal intensive care practices, namely the use of non-invasive methods of mechanical ventilation implemented in the last years, probably contributed to the better evolution of preterm infants with BPD.

Keywords

Bronchopulmonary dysplasia, preterm, newborns, neonatal intensive care, respiratory outcome.

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Introduction

Bronchopulmonary dysplasia (BPD) is a frequent complication in very preterm infants and its multifactorial etiology has not yet been fully established [1, 2]. Mechanical ventilation, inflammation/infection and oxidative stress are known as important risk factors, with prematurity beeing the most important factor, and the incidence of BPD is inversely proportional to gestational age and birth weight [3, 4].

The definition of BPD has been subjected to changes since its first description in 1967. Initially, BPD was described as a consequence of positive-pressure ventilation and oxygen therapy, which were responsible for severe histological lung lesions (inflammation, protein-rich edema, airway epithelial metaplasia, peribronchial fibrosis and hypertrophy of respiratory tract vascular smooth muscle): the "classic BPD" [5, 6].

Perinatal care has improved over the last decades and today very immature preterm infants have more chances to survive with BPD. These extremely low gestational age newborns are born in the course of the late canalicular or early saccular stages of lung development, causing disruption of the normal development of alveoli and vessels, despite gentle ventilation and less oxygen use, resulting in the "new BPD" [7]. Nowadays, although there is no effective treatment for BPD, preventive strategies are of great importance [8].

The aim of this study was to compare the clinical approach and their effects on BPD patients in the last two decades (1996-2005 vs. 2006-2015) in very preterm infants admitted in a level III neonatal intensive care unit (NICU).

Material and methods

All preterm infants with a birth weight ≤ 1,500 g and/or gestational age ≤ 32 weeks admitted between 1st January 1996 and 31st December 2015 to the NICU of Centro Hospitalar de São João, a level III center in the North of Portugal, were considered for this retrospective study.

We excluded all outborn neonates, children affected by major congenital anomalies, chromosomal anomalies and TORCH infections (Toxoplasmosis, Other [syphilis, varicella-zoster, parvovirus B19], Rubella, Cytomegalovirus and Herpes infections). The final study sample included 1,196 infants, wherein 96 (8%) had BPD. Infants were dichotomized into two groups according to the year of NICU admission (1996-2005 and 2006-2015).

Maternal, pregnancy and neonates clinical data were collected from clinical and informatics records, including: maternal age, infant's gender, gestational age (weeks), birth weight (grams), antenatal steroid pulses, mode of delivery, respiratory support in the delivery room and in the NICU, Apgar score at 1 and 5 minutes (< 7 vs. ≥ 7), exogenous surfactant therapy, oxygen therapy, major morbidity conditions – respiratory distress syndrome (RDS), BPD, pneumonia, pneumothorax, sepsis, meningitis, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), severe intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP), cystic periventricular leukomalacia (cPVL) –, length of mechanical ventilation, oxygen therapy, parenteral nutrition, NICU stay and survival.

The diagnosis and classification of BPD was defined according to the National Institutes of Health [9].

Gestational age (completed weeks) was assessed by menstrual age (women with regular menstrual cycles), ultrasound examination (when a discrepancy of two or more weeks existed between the gestational age calculated by menstrual dating and the age derived sonographically or in the absence of a menstrual date) [10] or the New Ballard Score (in the absence of obstetrical indexes) [11].

Small for gestational age was defined as a birth weight below the 10th centile of Fenton's fetal growth charts [12].

Early nasal continuous positive airway pressure (nCPAP) was considered if started in the first 15 minutes after birth and its failure was considered if patients needed invasive ventilation in the first 72 hours of life.

RDS diagnosis was made on a combination of clinical and radiographic features according to the criteria of RDS of the Vermont Oxford Network: PaO_2 < 50 mmHg in room air, a requirement for supplemental oxygen to maintain PaO_2 > 50 mmHg or to maintain a pulse oximeter saturation

over 85% within the first 24 hours of life, and a chest radiograph with reticulogranular appearance to lung fields with or without low lung volumes and air bronchograms within the first 24 hours of life.

Histological chorioamnionitis was defined according to Blanc's classification [13] and all the stages of chorioamnionitis were analyzed together.

Proven neonatal sepsis was defined as any systemic bacterial or fungal infection documented by a positive blood culture.

In all cases of preterm delivery whenever an infection cause could not be excluded, a combination of ampicillin and gentamicin was used as the first line antibiotic therapy, while waiting for the results of blood culture.

For the diagnosis and staging of NEC we used the modified criteria of Bell [14].

ROP was staged according to the international classification [15, 16].

IVH was classified according to Papile et al. [17], and grades III and IV were considered severe. cPVL was classified according to de Vries and Rennie [18]. Hemodynamically significant PDA was diagnosed considering echocardiographic findings performed by the pediatric cardiologist of the hospital [19]. The first evaluation was usually done between 24 and 72 hours of life with daily evaluations until closure of the ductus. The standard treatment was indomethacin until 2010, and ibuprofen afterwards.

Until 2003, the antenatal steroid regimen included dexamethasone (24 mg divided into two intramuscular doses 12 h apart). Since then, treatment has consisted of betamethasone (24 mg divided into two intramuscular doses 24 h apart) in pregnancies at risk of preterm labor between 24 and 35 weeks gestation.

Caffeine was routinely used in all preterm infants since the first day of life until 34 weeks of corrected age [20].

Oxygen was used to maintain saturations given by pulse oximetry in the range of 88-94% for RDS and ≥ 95% for established BPD until 2007. After this year, in preterm babies with RDS receiving oxygen, the saturation target was 90-95% [20].

Spontaneous breathing infants were stabilized with nCPAP of at least 5-6 cmH_2O via mask or nasal prongs. Intubation was used in infants who could not be stabilized with nCPAP [20].

Exogenous surfactant was administered for RDS by endotracheal tube in neonates on invasive mechanical ventilation or by INSURE (intubate-surfactant-extubate) in preterm infants on nCPAP requiring $FiO_2 > 0.40$ and/or arterial $PCO_2 > 65$ mmHg and pH < 7.20.

For non-invasive mechanical ventilation we used Infant Flow® SiPAP System (CareFusion, Yorba Linda, California, U.S.A.).

In 2003 we started to use volume guarantee with synchronized ventilatory modes (pressure support ventilation, synchronized intermittent mandatory ventilation or synchronized intermittent positive pressure ventilation), using Babylog® 8000 Plus, (Dräger, Lübeck, Germany) and posteriorly Fabian HFO® (Acutronic Medical Systems, Hirzel, Switzerland).

The DART protocol of dexamethasone was used in invasively ventilated patients that could not be weaned off after 10 days of life, after 2007 [21]. Before this time, we used the Cummings protocol [22].

Parenteral nutrition was started in the first day of life and enteral nutrition as soon as possible, according to the clinical stability of the patient. According to our protocol, parenteral nutrition starts with 70-80 ml/kg/day on the first day of life with daily increments of 10-15 ml/kg/day to a maximum of 150 ml/kg/day in the first week of life [23].

The study protocol was approved by the Ethics Committee of Centro Hospitalar de São João.

Statistical analysis

Descriptive statistics were presented using absolute and relative frequencies for categorical variables, mean and standard deviations (SD), and median and 25-75 percentiles (P25-P75) for normally and non-normally distributed continuous variables, respectively.

We compared two groups of infants, those who were admitted in 1996-2005 and those who were admitted in 2006-2015, using a Chi-square test or Fisher's exact test, as appropriate, when variables were categorical. For continuous variables Independent t-test (normally distributed variables) or Mann-Whitney U test (non-normally distributed variables) were used. A p-value below 0.05 was considered statistically significant. Crude and adjusted odds ratios (OR) and their respective 95% confidence intervals (CI) were calculated using logistic regression.

The statistical analysis was performed using SPSS® for Windows®, version 23.

Results

Of the 1,196 infants considered for this analysis, 229 (19.1%) died, 149 (23.3%) in the first decade (1996-2005) and 80 (14.4%) in the second (2006-2015) ($p < 0.001$). The prevalence of BPD decreased from 9.7% in 1996-2005 to 6.1% in 2006-2015 ($p = 0.023$) (**Tab. 1**).

Tab. 2 summarizes the maternal, pregnancy and BPD infants characteristics in both epochs. Overall, 68.8% of infants were male with a mean (SD) GA of 27.6 (0.22) weeks and a mean birth weight of 962.5 (33.89) grams. As reported in **Tab. 3**, there was a significant decrease in invasive mechanical ventilation median duration (39.50 days in 1996-2005 and 20.00 in 2006-2015, $p = 0.013$) and a

Table 1. Admissions, deceased and bronchopulmonary dysplasia (BPD) patients according to the two epochs (1996-2005 vs. 2006-2015).

	Total	1996-2005	2006-2015	p-value
NICU admissions, n (%)	1,196 (100)	640 (53.5)	556 (46.5)	**0.047**[a]
Deceased, n (%)	229 (19.1)	149 (23.3)	80 (14.4)	**< 0.001**[a]
Deceased and/or survivors with BPD, n (%)	325 (27.2)	211 (33.0)	114 (20.5)	**< 0.001**[a]
Survivors with BPD, n (%)	96 (8.0)	62 (9.7)	34 (6.1)	**0.023**[a]

NICU: neonatal intensive care unit; BPD: bronchopulmonary dysplasia.
[a]Chi-square test.

Table 2. Maternal, prenatal, and perinatal characteristics among infants with bronchopulmonary dysplasia (BPD) by period of NICU admission (1996-2005 vs. 2006-2015).

	Total (n = 96)	1996-2005 (n = 62)	2006-2015 (n = 34)	p-value
Sex, n (%)				
Male	66 (68.8)	43 (69.4)	23 (67.6)	0.863[a]
Female	30 (31.3)	19 (30.6)	11 (32.4)	
Gestational age, mean (± SD) (weeks)	27.63 (0.220)	27.74 (0.250)	27.41 (0.425)	0.475[d]
Birth weight, mean (± SD) (grams)	962.53 (33.891)	995.42 (40.065)	902.56 (61.292)	0.192[d]
Small for gestational age, n (%)	22 (22.9)	10 (16.1)	12 (35.3)	**0.033**[a]
Less than 1,000 g, n (%)	63 (65.6)	38 (61.3)	25 (73.5)	0.227[a]
Maternal age, median (min-max) (years)	31.00 (16-42)	30.50 (16-42)	31.00 (20-39)	0.979[c]
Preeclampsia, n (%)	21 (21.9)	9 (14.5)	12 (35.3)	**0.019**[a]
Change in umbilical flows, n (%)	17 (17.7)	6 (9.7)	11 (32.4)	**0.005**[a]
Change in cerebral flows, n (%)	16 (16.7)	6 (9.7)	10 (29.4)	**0.013**[a]
Antenatal steroids, n (%)	87 (90.6)	55 (88.7)	32 (94.1)	0.485[b]
Full cycle	56 (65.9)	29 (54.7)	27 (84.4)	**0.005**[a]
Histological chorioamnionitis, n (%)	24 (25.8)	14 (23.7)	10 (29.4)	0.546[a]
Delivery mode, n (%)				
Vaginal	32 (33.3)	25 (40.3)	7 (20.6)	0.050[a]
C-section	64 (66.7)	37 (59.7)	27 (79.4)	
Apgar score, n (%)				
1st minute < 7	73 (76.0)	48 (77.4)	25 (73.5)	0.669[a]
5th minute < 7	26 (22.7)	12 (20.0)	14 (41.2)	**0.027**[a]
Respiratory management in the delivery room, n (%)				
Spontaneous ventilation	3 (3.1)	2 (3.2)	1 (2.9)	0.999[b]
Endotracheal intubation	84 (87.5)	60 (96.8)	24 (70.6)	**< 0.001**[b]
Early nCPAP	15 (15.6)	1 (1.6)	14 (41.2)	**< 0.001**[b]

nCPAP: nasal continuous positive airway pressure.
[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test, [d]Independent t test.

Table 3. Morbimortality and management of infants with bronchopulmonary dysplasia (BPD), by period of NICU admission (1996-2005 vs. 2006-2015).

	Total (n = 96)	1996-2005 (n = 62)	2006-2015 (n = 34)	p-value
RDS, n (%)	88 (91.7)	55 (88.7)	33 (97.1)	0.253[b]
Surfactant administration, n (%)	81 (84.4)	51 (82.3)	30 (88.2)	0.563[b]
Surfactant doses, median (min-max)	2.00 (1-5)	2.00 (1-3)	2.00 (1-5)	0.361[c]
Invasive mechanical ventilation, n (%)	90 (93.8)	60 (96.8)	30 (88.2)	0.181[b]
Invasive mechanical ventilation, median (min-max) (days)	30.50 (1-211)	39.50 (1-211)	20.00 (2-138)	**0.013**[c]
nCPAP, n (%)	82 (85.4)	50 (80.6)	32 (94.1)	0.128[b]
nCPAP, median (min-max) (days)	32.00 (1-161)	22.50 (1-161)	45.50 (7-76)	**< 0.001**[c]
Oxygen, n (%)	96 (100)	62 (100)	34 (100)	-
Oxygen, median (min-max) (days)	70.00 (22-260)	69.00 (28-260)	71.50 (22-191)	0.412[c]
BPD, n (%)				
Mild/Moderate	70 (72.9)	43 (69.4)	27 (79.4)	0.458[a]
Severe	26 (27.1)	19 (30.6)	7 (20.6)	
PDA, n (%)	65 (67.7)	43 (69.4)	22 (64.7)	0.641[a]
With medical treatment	59 (95.2)	37 (94.9)	22 (95.7)	0.999[b]
With surgical treatment	10 (16.1)	4 (10.3)	6 (26.1)	0.153[b]
Nosocomial sepsis, n (%)	74 (77.1)	52 (83.9)	22 (64.7)	**0.033**[a]
NEC ≥ 2a, n (%)	3 (3.1)	3 (4.8)	0 (0)	0.550[b]
ROP ≥ 2, n (%)	29 (30.2)	14 (22.6)	15 (44.1)	**0.028**[a]
IVH ≥ III, n (%)	21 (21.9)	8 (12.9)	13 (38.2)	**0.004**[a]
cPVL, n (%)	7 (7.3)	4 (6.5)	3 (8.8)	0.695[b]
Parenteral nutrition, n (%)	95 (99.0)	61 (98.4)	34 (100)	0.999[b]
Parenteral nutrition, median (min-max) (days)	36.00 (8-145)	40.00 (8-145)	33.0 (12-101)	0.070[c]
NICU stay, median (min-max) (days)	78.50 (21-259)	74.00 (29-259)	86.00 (21-191)	0.191[c]
Sequels, n (%)				
O_2 requirement	25 (30.1)	14 (26.4)	11 (36.7)	0.328[a]
Tracheostomy	2 (2.4)	1 (1.9)	1 (3.3)	0.999[b]
No feeding autonomy	1 (1.2)	1 (1.9)	0 (0)	0.999[b]
Jejune/ileostomy	1 (1.2)	1 (1.9)	0 (0)	0.999[b]
Ventriculoperitoneal shunt	2 (2.4)	0 (0)	2 (6.7)	0.128[b]
Deceased, n (%)	13 (13.5)	9 (14.5)	4 (11.8)	0.999[b]

[a]Chi-square test; [b]Fisher's exact test; [c]Mann-Whitney U test.
RDS: respiratory distress syndrome; nCPAP: nasal continuous positive airway pressure; BPD: bronchopulmonary dysplasia; PDA: patent ductus arteriosus; NEC: necrotizing enterocolitis; ROP: retinopathy of prematurity; IVH: intraventricular hemorrhage; cPVL: cystic periventricular leukomalacia; NICU: neonatal intensive care unit.

significant increase in nCPAP duration (22.50 days in 1996-2005 and 45.50 days in 2006-2015, $p < 0.001$). ROP grade ≥ 2 and severe IVH had a significant increase in the second decade (22.6% vs. 44.1% [$p = 0.028$] and 12.9% vs. 38.2% [$p = 0.004$], respectively). There was a significant lower prevalence of nosocomial sepsis in the second decade (83.9% vs. 64.7%, $p = 0.033$).

Infants admitted during the second epoch were more likely to have ROP grade ≥ 2 (OR = 8.112, 95%CI: 1.396-47.134; $p = 0.020$) and severe IVH (OR = 12.313, 95%CI: 1.921-78.920; $p = 0.008$).

Discussion

In the last decades there have been several changes in perinatal care around the world with a consequent implementation of better clinical practices during pregnancy as well as in management of the preterm infants. Our center accompanied these changes showing an improvement in morbimortality of these very preterm infants.

There has been a statistically significant increase in pregnancy-associated pathologies as

preeclampsia and cerebral and umbilical flows changes, which may be related to the birth of more small for gestational age infants and consequently with more severe neonatal outcome. However, part of this increase may be due to a better prenatal screening over the last years.

Although some studies showed that hypertensive diseases during pregnancy are a protective factor for major IVH [24, 25], our results did not show a decrease in IVH despite the observed increase of hypertensive diseases on pregnancy.

At the end of the twentieth century, the National Institutes of Health and the American College of Obstetricians and Gynecologists published a consensus statement defending the use of antenatal steroids in preterm deliveries of 24 to 34 weeks of gestational age in order to induce fetal maturation and reduce the risks for RDS, IVH and neonatal death [26]. According to our results the number of completed antenatal steroids cycles increased since 2006, showing improvement on obstetrical practices.

The admission of more small for gestational age infants and preterm newborns with lower Apgar scores at 5 minutes in the second decade among the BPD patients can explain the increase in prevalence of ROP and IVH.

Despite the clear admission of more severe patients in the second decade, we found a statistically significant decrease in invasive mechanical ventilation use (and in its duration) and an increase in the use and duration of non-invasive mechanical ventilation (nCPAP). Also, at the delivery room, there was a higher prevalence of use of early nCPAP, and this fact highlights better neonatal practices [27]. Invasive mechanical ventilation is a well-known risk factor for the development of BPD and all efforts must be done to implement non-invasive mechanical ventilation in this high-risk group of preterm infants [3, 28].

Another fact that reinforces the improvement in practices in perinatal and neonatal care at our center is the statistically significant decrease of nosocomial sepsis prevalence, a fact already reported in another study [29]. The importance of this data was highlighted in a recent multicenter study showing that sepsis is one of the most common causes of deaths in NICUs [30] and BPD development [3, 28].

With regard to BPD severity, our data show that there was a lower proportion of severe BPD diagnosed in the second decade of the study. Probably, in the first ten years of the study, severe BPD was related to the greater use of invasive mechanical ventilation.

Although there were no significant differences in gestational age and birth weight between the two periods of our study, in the second one more severe patients were admitted, proven by worse Apgar scores as mentioned previously. As we have shown before, clinical practices in neonatal intensive care units differ one from the other and benchmarking among them it's crucial to improve outcomes [31].

With respect to clinical status, at discharge there were no significant differences between the two epochs. Taking into account that in the second decade more severe infants were admitted, this seems to be encouraging information.

There are some major limitations of this study. It is a single center study and so the results cannot be generalized. Its retrospective nature makes it difficult to obtain data, especially those from the first period. We included preterm neonates with less than 32 weeks of gestational age. Recently, most of the studies have focused on newborns with gestational age less than 29 weeks, because the 29-32 weeks neonates are at a lower risk of morbidity and mortality. This aspect should be taken into account when comparing the results.

Anyway, the strength of our study is that it shows a decrease in BPD prevalence and mortality associated to an increase in the use of early nCPAP and non-invasive ventilation practices, along with a decrease of nosocomial sepsis prevalence.

In conclusion, the improvement in perinatal and neonatal intensive care practices implemented over the last years, contributed to the better evolution of our preterm infants. Moreover, even in the absence of an effective therapy for BPD, professionals should be sensitized to the preventive management of these preterm infants.

Declaration of interest

The Authors report no conflicts of interest.

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