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ORIGINAL

Prenatal and postnatal risk factors for developing bronchopulmonary dysplasia

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ABSTRACT

Aim. To determine prenatal and postnatal risk factors for developing bronchopulmonary dysplasia in infants < 30 weeks of gestational age.

Methods. Over a 22-month period, 115 newborns were enrolled in the study. Details including gestational age, sex, birth weight, prenatal steroids, surfactant treatment, ventilatory support, days of postnatal oxygen requirement, late onset sepsis/pneumonia, air leaks, patency of ductus arteriosus, and fluid intake were collected. The presence of chorioamnionitis was diagnosed by histological examination. Commercial ELISA kits were used for the determination of the IL-6 and IL-8 levels.

Results. Twenty-five infants developed BPD and 90 were enrolled in the non BPD group. Lower gestational age and male sex increased the risk for BPD. There was no difference in the presence of chorioamnitis and the level of IL-6 and IL-8 measured in cord blood and gastric aspirate between the groups. Intubation in the delivery room (resuscitation), need for surfactant treatment, mechanical ventilation, late onset sepsis/pneumonia, increased oxygenation index increased the risk for BPD after adjustment for GA and gender.

Conclusion. In our cohort of infants with GA < 30 weeks exposure to prenatal inflammation did not increase the risk for BPD. However, low gestational age, male sex, need for resuscitation, mechanical ventilation and late onset sepsis were major risk factors for BPD development.

Key words: premature infant, bronchopulmonary dysplasia, respiratory distress syndrome, chorioamnionitis, interleukin 6, interleukin 8

Introduction

Bronchopumonary dysplasia (BPD) was first described by Northway in 1967 (1) reporting clinical and radiographic changes in the lungs of preterm infants who had respiratory distress syndrome (RDS) and who were treated with oxygen and mechanical ventilation. Beside risks of mechanical ventilation (duration, volu-, barotrauma and oxidative stress) also nosocomial infections and patent ductus arteriosus had been clearly identified as risk factors for BPD development (2,3,4). The study from Watterberg et al. (5) in 1996 established that that the presence of chorioamnionitis (CHA) was associated with lower incidence of RDS and higher of BPD, indicating that lung injury can start before birth. Later studies confirmed that CHA (6,7,8) funisitis (9), and fetal inflammatory response syndrome (10,11) were associated with increased incidence of BPD; however, results were not reproduced in some later studies (12,13). It has been suggested that the association between CHA and BPD is more complicated (14). Van Marter et al. (15) introduced "multiple hit" theory. They established that CHA does not increase the incidence of BPD by itself, but only

in combination with already known risk factors for BPD, such as mechanical ventilation longer than 7 days and exposure to postnatal infection.

Most of the published studies were focused on identifying either prenatal or postnatal risk factors. The aim of this study was to identify prenatal and postnatal risk factors in a cohort of infants with GA < 30 weeks.

Material and methods

All infants delivered at less than 30 weeks of gestation in the Ljubljana Maternity Hospital, a tertiary referral centre for premature infants in Slovenia, during the period from September 1st, 2000, to June 30th, 2002, were enrolled in the study. The eligibility criteria were: 1) inborn infant, 2) availability of placenta and cord blood, 3) written informed parental consent obtained, and 4) absence of obvious congenital malformation. The National Medical Ethics Committee approved the study. Details including gestational age, sex, birth weight, prenatal steroids, fluid intake, blood pressure, catecholamine, indomethacin and surfactant treatment, ventilatory support and days of postnatal oxygen requirement were collected. Gestational age was determined by the best obstetric estimate using the last menstrual period and/or early ultrasound assessment.

The placenta, including fetal membranes and umbilical cord, was examined microscopically for the presence of inflammation. CHA was defined as acute when ten or more polymorphonuclear leukocytes were found per high-power field in the amniotic and chorionic membranes, in the chorionic plate, and/or in the umbilical cord. Blood was collected from the umbilical cord immediately after birth, then centrifuged and stored at –70°C until cytokine immunoassay was performed. Commercial ELISA kits (Endogen-Pierce, Boston, USA) were used for determination of the IL-6 and IL-8 levels.

Gastric aspirate sample was collected at the time of delivery with a 5F orogastric feeding tube. Because of no reliable correction factor available (16), cytokine concentrations in gastric aspirates were expressed as volume concentrations (pg/ml or ng/ml).

Infants with RDS on artificial ventilation ($FiO_2 > 0.60$ and oxygenation index (OI) > 20 ($OI = (MAP \times FiO_2 \times 100)/p_aO_2$, MAP mean airway pressure, FiO_2 fraction of inspired oxygen, p_aO_2 partial pressure of oxygen in arterial blood) were treated with exogenous surfactant (poractant alpha, Curosurf®, 100 mg/kg body weight). Pulmonary air leak (PAL) was confirmed by X-ray. Late onset sepsis/pneumonia (LOS/P) was confirmed by isolation of the organism from the blood or cerebrospinal fluid/tracheal aspirate later than 72 hours of life. Patent ductus arteriosus (PDA) was diagnosed clinically and confirmed by echocardiography.

BPD was diagnosed according to National Information Health Center as oxygen dependency at 36 weeks of GA. Target saturation was kept between 88-92 %.

Statistical analysis. The T-test or Mann-Whitney U test were used for comparison of continuous variables that were normally or not normally distributed. The Pearson chi-square test or Fisher's exact test (both 2-sided) were used for comparison of categorical variables as appropriate. Logistic regressions were performed stratified by GA. The results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) or odds ratio (OR) with a 95 % confidence interval (CI). P value < 0.05 was selected to determine statistical significance. Statistical Package of Social Sciences, version 14.0 (SPSS Inc., Chicago, USA) was used for the statistical analyses.

Results

One hundred and fifteen infants (89.1 %) with GA < 30 weeks survived and met the eligibility criteria, from a total of 129 born during the study period. Among the survivors, 25 (21.7 %) infants developed BPD. Male infants comprised 53.0 % of the study group. Mean 1-minute Apgar score was 6 (range, 4–7) and mean 5-minute Apgar score was 7 (range, 6–8). Ninety-three (80.8%) infants received prenatal corticosteroids (39 incomplete and 54 complete courses).

General characteristics of the study group are shown in Table 1. Infants who developed BPD had lower birth weight and gestational age. The percentage of males was higher in the BPD group. The average length of hospitalization was 1.7 times longer in the BPD group when compared to the non BPD group, despite the average difference in GA between the groups being 1 week only. The mode of delivery, prenatal corticosteroid therapy, 1 and 5 min Apgar score and number of multiples did not differ between the groups. Figure 1 shows percentages for death, survival with BPD, and survival without BPD for each week of gestational age. In the group of infants with GA ≤ 24 weeks, survival without BPD was very low (7.1 %). This was followed with progressive increase in survival without BPD for each week of GA; survival without BPD in the group of infants with GA of 29 weeks already reached 83.3 %.

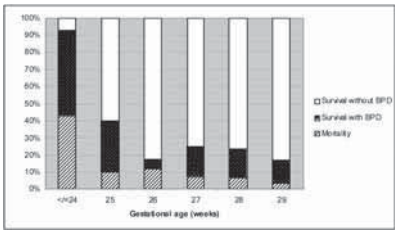
Table 2 shows the comparison of the level of measured cytokines between the BPD and non BPD group. There was no difference in clinical, histological chorioamnionitis, and funisitis between the study groups. The level of IL-6 and IL-8 in cord blood and gastric aspirate was also similar in both study groups. Separate analysis of all infants with analyzed placenta for the presence of histological chorioamnionitis showed that infants with histologicaly confirmed chorioamnionitis after adjustment for GA less likely developed RDS (OR 0.32 [0.14–0.76], p=0.009), however there was no difference in the development of BPD.

Table 3 shows the difference in resuscitation measures and ventilatory support between infants with BPD and infants without BPD. Infants who developed BPD were more often resuscitated in the delivery room, more often needed intubation and surfactant treatment. Infants who developed BPD were ventilated with higher maximal peak inspiratory pressure (MIP), and needed higher FiO2. The length of mechanical ventila-

Table 1. Characteristics of infants with and without BPD. Results as percentage (%) or mean (SD).

	No BPD (n=90)	BPD (n=25)	p
Birth weight (g)	1088 (212)	841 (216)	<0.001
GA (wks)	27.5 (1.3)	26.4 (1.9)	0.001
male (%)	40.7	66.7	0.027
1-minute Apgar score<3 (%)	6.7	12.0	0.30
5-minute Apgar score<5 (%)	6.7	4.0	0.52
Prenatal dexamethason (%)	81.1	80.0	1.0
Vaginal delivery (%)	56.7	64.0	0.64
Multiple pregnancies (%)	25.1	32.6	0.61
Hospital days	63 (16)	110 (24)	<0.001

GA, gestational age; BPD bronchopulmonary dysplasia.



BPD , bronchopulmonary dysplasia; GA, gestational age.

Figure 1. Mortality and survival in infants with/without BPD with respect to GA at birth.

tion and oxygen supplementation was significantly longer in the BPD group when compared to non BPD group. Infants who developed BPD also had more PAL and more often suffered from LOS/P.

Table 4 shows that infants who developed BPD had more often echocadiographically confirmed PDA and had higher fluid intake on day 2 when compared to infants without BPD. The need for cathecholamine treatment was also higher in the BPD group.

Risk factors for BPD development calculated with regression multivariate model are presented in Figure 2. Factors that independently increased risk for BPD development were: need for intubation in the delivery room, level and length of mechanical ventilation support (MAP, MIP, OI), need for surfactant replacement treatment, the presence of PDA, and development of LOS/P.

Discussion

In our cohort of infants with GA < 30 weeks, prenatal and postnatal risk factors for BPD development were studied. As expected, the risk for BPD declined with increased gestational age. Prenatal inflammation (chorioamnionitis and exposure to cytokines) did not increase the risk for BPD development. Need for resuscitation with early intubation in the delivery room, need for surfactant replacement treatment, the length and level of ventilatory support, development of LOS/P, and the presence of PDA increased the risk for BPD.

Male gender increases the risk for death in low birth weight populations (17). Increased incidence of BPD in males can be partly explained by higher oxidative stress and lower antioxidant activity in male preterms (18).

Previously published data show that low gestational age (the stage of pulmonary development) is one of the crucial risk factors for BPD development. In animal studies, it was established that intra-amniotic application of endotoxin on the one hand induces maturation of fetal lungs but on the other hand inhibits alveolarisation of the lungs and causes muscularisation of the media and collagen deposition in the adventitia of small pulmonary arteries (19). These results support the "Watterberg effect" (5). Studies confirming association between BPD and CHA are mainly from the time when the use of prenatal steroids was low. The overview through the studies on prenatal inflammation and BPD showed significant variations in gestational age and birth weight ditribution, the percentage of prenatal steroid and surfactant treatment. It is well known that the incidence of CHA and respiratory symptoms increase with lower GA. Most of the recently published studies on choriamnionitis and BPD have not confirmed the effect of chorioamnionitis on BPD. Our results have shown no influence of CHA, neither funisitis or elevated levels of cytokines on BPD, but have also shown that prenatal exposure to CHA decreases incidence of RDS, results similar to other published data (20,21,22,23). Moss et al.(24) showed in a sheep model that lung structure, function, and surfactant system were all significantly affected by the intra-amnioticaly given endotoxin at all stages of pulmonary development, but the response itself differed depending on the gestational timing. The exposure to prenatal inflammation increases surfactant synthesis and decreases RDS development (25). In sheep, lung maturation characterized by increased lung volumes and alveolar saturated phosphatidylcholine, occurred at 7 days after the endotoxin injection and persisted for 25 days (26). Despite the initial assumption that prenatal inflammation reduces the risk for RDS by eliciting a fetal cortisol surge, Jobe et al (27) showed in a fetal sheep model that early lung maturation induced by intra-amniotic endotoxin occurred without an increase in fetal plasma cortisol, which indicated that endotoxin promoted lung maturation by a mechanism independent of cortisol. Morphometric lung analyses in the sheep model showed that alveolar wall thickness was reduced in the sheep treated with endotoxin at the time of transition to the canalicular stage (25). Kramer at al. (28)

Table 2. Comparison of the level of measured cytokines between the groups. Results as percentage or median with inter quartile range (IQR).

	No BPD (n=90)	BPD (n=25)	p
Clinical CHA (%)	22.2	24.0	0.85
Histological CHA (%)	43.0	43.7	0.96
Funisitis (%)	32.9	32.0	0.59
IL−6 cord blood (pg/ml)	6.0 (1.9 − 23.2)	3.4 (1.2 − 28.2)	0.80
IL−8 cord blood (pg/ml)	306 (98 − 1033)	424 (107 − 902)	0.92
IL−6 gastric aspirate (ng/ml)	3.4 (0.5 − 13.5)	2.7 (0.3 − 14.1)	0.66
IL−8 gastric aspirate (ng/ml)	21 (5 − 278)	31 (6 − 464)	0.93

CHA, chorioamnionitis; IL-6, interleukin-6; IL-8, interleukin-8.

Table 3. Differences in resuscitation measures and ventilatory support between infants without and with BPD. Results as percentage (%) or mean (SD).

	No BPD (n=90)	BPD (n=25)	p
Resuscitation in DR (%)	34.4	92.0	0.003
Intubation in DR (%)	6.7	24.0	0.022
Mechanical ventilation (%)	38.9	100	<0.001
Surfactant (%)	34.5	92.0	<0.001
PAL (%)	3.5	20.0	0.014
LOS/P (%)	10.4	68.0	<0.001
Max MIP (cm H2O)	21.9 (4.9)	25.3 (4.8)	0.012
Max PEEP (cm H2O)	3.5 (1.1)	3.7 (1.2)	0.48
Max MAP (cm H2O)	9.8 (2.5)	11.8 (2.2)	0.030
Max OI	12.0 (8.6)	18.9 (10.0)	0.013
Max FiO2;	49.6 (24.9)	69.3 (23.5)	0.002
Days of mechanical ventilation	7.1 (8.8)	37.1 (19.1)	<0.001
Days on oxygen	20 (20)	105 (26)	<0.001
First breathing room air (days)	4.5 (6)	62 (60)	<0.001

DR, delivery room; FiO_2, fraction of inspired oxygen; LOS/P, late onset sepsis/pneumonia; MAP, mean airway pressure; MIP, maximal inspiratory pressure; OI, oxygenation index; PAL, pulmonary air leak; PEEP, positive end-expiration pressure

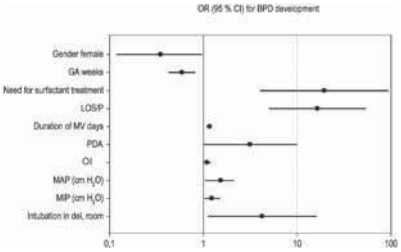
showed in bitransgenic mice that perinatal increase in TGF-α disrupted the saccular phase of lung morphogenesis and caused remodeling, characterized by mesenchymal thickening, vascular remodeling, and poor apposition of capillaries to distal air spaces after; however, surfactant levels were not reduced. Pathological changes in TGF-α-overexpressing mice bore similarities to premature infants born in the saccular phase who developed BPD. In addition to results from animal experiments, very similar results were found in a clinical study from Viscardi et al (29). They found that histological CHA was significantly associated with BPD in infants less than 28 weeks gestation at birth, but not in infants with gestational age above 28 weeks. The percentage of CHA in our study was in the range of previously published studies. As shown in overview from Beer and Zimmerman (30), the increased incidence of BPD after prenatal inflammation was reproduced in 6 of 18 studies; furthermore, in only one study the results were adjusted for gestational age (31). Beside the importance of when the fetus is exposed to prenatal inflammation, the time of exposure to the intra-amniotic endotoxin is also important. Kallapur et al (32) established that continuous exposure to the intra-amniotic endotoxin, in contrast to single, did not cause sustained structural abnormalities in fetal sheep lungs. The most probable reason for not confirming positive association between prenatal inflammation and BPD in our study was high percentage of prenatal steroids, as already suspected in the overview of Beer and Zimmerman (30). Similarly to other clinical settings it was also impossible to quantify the duration of fetal exposure to infection and inflammation.

The association of BPD and mechanical ventilation is well described. Artificial ventilation is causing damage with high peak inspiratory pressures and high percentage of inhaled oxygen, causing the formation of oxygen radicals. Beside GA, gender and PDA, resuscitation measures and mechanical ventilation

Table 4. Patent ductus arteriosus, indomethacin and cathecholamine treatment and fluids during first three days in infants without and with BPD. Results in percentage (%) or mean (SD).

	No BPD (n=90)	BPD (n=25)	p
PDA (%)	13.3	76.0	0.007
Indomethacin prophylactic (%)	61.3	92.0	0.006
Catecholamine treatment (%)	15.6	36.0	0.04
Day 1 fluids (ml/kg BW)	89 (15)	92 (11)	0.32
Day 2 fluids (ml/kg BW)	96 (10)	102 (13)	0.03
Day 3 fluids (ml/kg BW)	106 (10)	107 (14)	0.56
Weight loss on day 3 (%)	10.3	7.8	0.11

PDA, persistent ductus arteriosus; BW, body weight



BPD, bronchopulmonary dysplasia; GA, gestational age; LOS/P, late onset sepsis/pneumonia; MAP, mean airway pressure; MIP, maximal inspiratory pressure; OI, oxygenation index; OR, odds ratio; MV, mechanical ventilation; PDA, patent ductus arteriosus

Figure 2. OR (95 % CI) for BPD development in our cohort of infants with GA < 30 weeks (variable adjusted for GA and gender).

were the major risk factors contributing to BPD development. In animal models it was shown that already few manual breaths with high tidal volumes may damage immature lungs (33). Artificial ventilation is one of the oldest known risk factors for BPD. It is damaging to the lung either at too low or too high tidal volumes. Every additional day on conventional mechanical ventilation also increased the risk for BPD development significantly.

The presence of symptomatic PDA was associated with higher risk for BPD (34,35). Left to right shunt through PDA produces an increase in pulmonary blood flow and in lung fluid, negatively affecting lung function and gas exchange. The incidence of PDA was significantly higher in the BPD group than in non BPD group and PDA was shown to be independent risk factor for BPD development also in our study. The intake of fluids on day 2 was also significantly higher in the BPD group when compared to the non BPD group. The effect of fluids on BPD development was probably indirect through keeping the PDA open (36).

In mice intermittent hypoxic stress increases hyperoxia induced damage of lung tissue and exacerbates alveolar developmental arrest (37). There are similarities between inflammation and hypoxia/reoxygenation, since both activate a number of inflammatory mediators such as cytokines and adhesion molecules, some of which are found in high concentrations in tracheal aspirate fluid of infants developing BPD (38).

Analysing prenatal and postnatal risk factors for BPD in our cohort of infants with GA < 30 wks, prenatal inflammation was not identified as a risk factor for BPD. Beside already known measures of how to decrease the incidence of BPD (prenatal corticosteroid treatment, early surfactant treatment) we should work further on 1) prevention of preterm birth, 2) additional studies on the resuscitation of preterm infants, 3) shortening the time of mechanical ventilation, 4) alternative ventilation strategies, 5) monitoring and treatment of oxidative stress during mechanical ventilation, 6) prevention of postnatal sepsis/pneumonia, and 7) monitoring for hemodynamic PDA.

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