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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Effect of Initial Mode of Respiratory Support on Bronchopulmonary Dysplasia in Extremely Low Birth Weight Preterm Infants

Aşırı Düşük Doğum Ağırlıklı Prematüre Bebeklerde Başlangıç Solunum Desteğinin Bronkopulmoner Displazi Üzerine Etkisi

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Abstract

Objectives: Despite improvements in neonatal care and survival of preterm infants, the incidence of bronchopulmonary dysplasia (BPD) is not decreasing. The aim of this study was to evaluate the impact of initial mode of respiratory support on BPD in extremely low birth weight (ELBW) infants.

Materials and Methods: ELBW infants admitted to neonatal intensive care unit were analyzed retrospectively between 2014 and 2017. The effects of initial respiratory support options and morbidities on BPD were evaluated between infants who developed BPD or not.

Results: Total 101 infants were evaluated, and 68 were included. For those whose incidence of BPD was 46%, the mean gestational age and birth weight were 27.8±1.8 weeks and 814±118 g, respectively. Patients with BPD (n=31) had a lower mean gestational age and birth weight, higher rates of necrotizing enterocolitis and retinopathy of prematurity (p<0.001, p=0.012, p=0.024, and p=0.018, respectively). Requirement of surfactant and need for invasive respiratory support initially after birth were found to be major risk factors for BPD. The duration of invasive ventilation after birth was longer in patients with BPD (p=0.034). BPD or death occurred in 66 of 101 infants. Infants received non-invasive respiratory support after birth had a lower risk for BPD, and BPD or death.

Conclusion: To prevent the development of BPD in ELBW infants, the respiratory support should be non-invasive after birth, and if the infant is intubated, duration of invasive respiratory support should be shortened for less than 3 days.

Key Words: Preterm, Infant, Bronchopulmonary Dysplasia, Extremely Low Birth Weight, Respiratory

Öz

Amaç: Yenidoğan bakımındaki gelişmelere ve prematüre bebeklerin sağkalım oranlarında artışa rağmen bronkopulmoner displazi (BPD) sıklığı azalmamaktadır. Bu çalışmanın amacı, aşırı düşük doğum ağırlıklı (ADDA) bebeklerde solunum desteği başlangıç yönteminin BPD üzerine etkisini değerlendirmektir.

Gereç ve Yöntem: 2014-2017 yılları arasında yenidoğan yoğun bakım ünitesine yatırılan ADDA bebekler geriye dönük olarak analiz edildi. BPD gelişen veya gelişmeyen bebeklerde başlangıç solunum desteği yöntemleri ve morbiditelerin BPD üzerine etkisi değerlendirildi.

Bulgular: Değerlendirilen toplam 101 bebeğin 68'i dahil edildi. BPD sıklığı %46 olarak saptanan bebeklerin ortalama gebelik haftası 27,8±1,8 hafta ve doğum ağırlığı 814±118 g idi. BPD'li hastaların (n=31) gebelik haftası ve doğum ağırlığı daha düşük, nekrotizan enterokolit ve prematüre retinopati sıklığı daha yüksekti (sırasıyla p<0,001, p=0,012, p=0,024 ve p=0,018). Sürfaktan gereksinimi ve doğumdan sonra invaziv solunum desteği

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gereksiniminin BPD gelişimi için majör risk faktörleri olduğu saptandı. İnvaziv ventilasyon süresi BPD'li hastalarda daha uzundu (p=0,034). BPD veya ölüm, 101 bebeğin 66'sında gelişti. Yaşamın ilk gününde non-invaziv solunum desteği almanın BPD ve BPD veya ölüm riskini azalttığı saptandı.

Sonuç: ADDA'lı bebeklerde BPD'yi önlemek için, doğum sonrası başlangıç solunum desteği non-invaziv olmalı ve eğer bebek entübe ise invaziv solunum desteği süresi 3 günden kısa olmalıdır.

Anahtar Kelimeler: Prematüre, Bebek, Bronkopulmoner Displazi, Aşırı Düşük Doğum Ağırlığı, Solunum

Introduction

Bronchopulmonary dysplasia (BPD) is one of the most important morbidities of prematurity occuring in approximately 50% of with extremely low birth weight (ELBW) preterm infants. Although the survival of extremely low gestational age newborns (ELGANs) has increased with the improvements in perinatal and neonatal care, the incidence of BPD has not changed in recent years (1-4).

There are many potential risk factors for BPD that described in the literature. Chorioamnionitis, maternal hypertension, and intrauterine growth restriction have been identified as the most common antenatal risk factors; degree of immaturity both as gestational age (GA) and BW, male gender, APGAR score, and resuscitation maneuvers as perinatal risk factors; respiratory distress syndrome (RDS), sepsis, air leak, inadequate nutrition, patent ductus arteriosus, oxygen therapy, and greater levels of respiratory support as postanatal risk factors (5-9).

Mechanical ventilation (MV) is a life-saving practice in all infants, but may cause severe damage. An association was shown between the barotrauma and volutrauma induced by MV and the alterations of lung tissue in experimental studies (10,11). The total duration of MV is a predictive finding for the development and severity of BPD. The longer the infant is intubated, the higher the risk of developing BPD. So, it is recommended that if intubated, the infant should be extubated as soon as the low ventilator seetings are reached. Understanding the clear link between the MV and the risk of developing BPD has led to wide-spread use of non-invasive ventilation techniques in preterm infants (12-14).

In this study, it is aimed to evaluate the impact of initial respiratory support option as a risk factor for BPD in ELBW preterm infants.

Materials and Methods

This retrospective, cohort study includes a single tertiary center with 30-bed capacity which takes care of high-risk infants of approximately 5,000 annual inborn deliveries and approximately 1,000 annual admissions and high-risk referrals from all parts of Turkey.

We included the data of all ELBW infants between January, 2014 and December, 2017. Outborn infants and infants with major congenital malformations or identifiable syndromes were excluded. The Ethics Committee of Ankara University Faculty of Medicine evaluated and approved the study (approval no: 18-1212-18).

These infants were divided into BPD group and without BPD group according to BPD diagnostic criteria which was developed by Jobe and Bancalari (15) considering infants' GA, need for oxygen and ventilatory support. Infants born at <32 weeks' gestation and required oxygen >21% for at least 28-days were classified, according to their respiratory status at 36 weeks' postmenstrual age (PMA): if with room air defined as 'mild', if with oxygen requirement <30% defined as 'moderate', and if with requirement of oxygen >30%, and/or positive pressure ventilation and/or continous positive airway pressure defined as 'severe' BPD (15).

The medical records of 101 ELBW preterm infants were retrospectively reviewed. The clinical features of infants, the effects of respiratory support options and morbidities on BPD were compared between the infants who developed BPD and who did not among infants who survived to 36 weeks' PMA.

Infants who developed BPD at 36 weeks' PMA plus infants who died due any cause during hospitalization before they reached 36 weeks' PMA defined as BPD or death.

According to our neonatal intensive care unit (NICU) protocol, we initiate early continuous positive airway pressure (CPAP) in the delivery room for spontaneously breathing premature infants born ≤32 weeks' gestation. If the FiO_2 requirement >40% in infants with RDS findings while receiving non-invasive ventilation, surfactant therapy is considered.

Statistical Analysis

Student's t-test was used to compare populations, chi-square test was used to compare proportions. Continuous variables are shown as mean and standard deviation, whereas categorical variables are shown as number of cases and percentages. All statistics analyses were done using a standard statistical software (SPSS for Windows 15, Chicago, IL). Risk factors for BPD were analyzed with Logistic regression analysis. Threshold value according to the Youden index were calculated for the duration of invasive ventilation. The value at the highest

sensitivity and selectivity was determined as the threshold value. In all analyses, p<0.05 was taken to indicate statistical significance.

Results

The medical records of ELBW preterm infants who admitted to the NICU from January 2014 to December 2017 were evaluated. Among 101 infants, 68 survived to 36 weeks' PMA whose mean GA and BW were 27.8±1.8 weeks and 814±118 g, respectively (Figure 1).

The incidence of BPD was 46% among 68 enrolled patients. Patients with BPD (n=31) had a lower mean GA (26.7±1.6 vs 28.6±1.5 weeks, p<0.001) and BW (775±120 vs 847±117 g, p=0.012), higher rates of necrotizing enterocolitis (NEC) (19 vs 3%, p=0.024) and retinopathy of prematurity (ROP) (26 vs 5%, p=0.018) than in those without BPD (n=37) (Table 1).

Presence of RDS and requirement of surfactant, and need for invasive respiratory support initially after birth were found to be major risk factors for development of BPD (Table 2). Patients who received non-invasive respiratory support on the first day of life (DOL) had a lower risk for BPD [RR 0.34, 95% confidence interval (CI) 0.198-0.609, p<0.001]. The duration of invasive ventilation after birth was significantly longer in patients with BPD (p=0.034). The cut-off duration of invasive ventilation as a risk factor for development of BPD was 2.5 days (69% sensitivity and 70% specificity).

BPD or death occurred in 66 of 101 infants (65%). Patients with BPD or death had a lower mean GA (26.7±1.9 vs 28.6±1.5, p<0.001) and BW (737±143 vs 847±107 g, p<0.001).

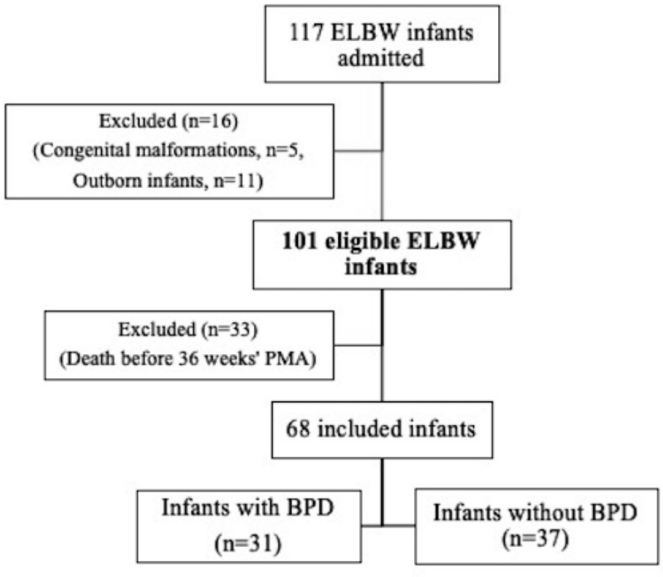

Figure 1: The flowchart of the study

BPD: Bronchopulmonary dysplasia, ELBW: Extremely low birth weight

Requirement of surfactant, need for invasive respiratory support initially after birth were associated with the occurrence of BPD or death (Table 2). The incidence of BPD or death decreased in infants who received non-invasive ventilation on the first DOL (RR: 0.201, 95% CI: 0.109-0.372, p<0.001).

Table 1: Characteristics and outcomes of infants with and without BPD survived to 36 weeks PMA

	Infants with BPD (n=31)	Infants without BPD (n=37)	p-value
Gestational age*, w	26.7±1.6	28.6±1.5	<0.001
Birth weight*, g	775±120	847±117	0.012
Gender (male), n (%)	16 (52)	14 (38)	0.25
Type of delivery (CS), n (%)	27 (87)	34 (92)	0.51
Multiple pregnancy, n (%)	10 (32)	11 (30)	0.82
Antenatal steroid, n (%)	25 (81)	25 (68)	0.421
RDS, n (%)	25 (81)	9 (24)	<0.001
Surfactant requirement, n (%)	25 (81)	9 (24)	<0.001
Invasive respiratory support at 1st DOLa, n (%)	26 (84)	13 (42)	<0.001
Non-invasive respiratory support at 1st DOLa, n (%)	5 (16)	18 (58)	<0.001
PDA, n (%)	14 (45)	9 (24)	0.07
PDA management, n (%)			
Conservative	3 (21)	1 (11)	0.52
Medical	11 (79)	8 (89)	
NEC, n (%)	6 (19)	1 (3)	0.024
IVH (gr ≥3), n (%)	5 (16)	3 (8)	0.307
ROP, n (%)	8 (26)	2 (5)	0.018
LOS, n (%)	13 (56)	10 (43)	0.19
Mortality, n (%)	2 (6)	2 (5)	0.85

*Data as mean ± SD

[a]Infants received any respiratory support (n=62)

BPD: Bronchopulmonary dysplasia, CS: Ceserean section, DOL: Day of life, IVH: Intraventricular hemorrhage, LOS: Late onset sepsis, NEC: Necrotizing enterocolitis, PDA: Patent ductus arteriosus, RDS: Respiratory distress syndrome, ROP: Retinopathy of prematurity

Table 2: Multivariate regression of factors associated with BPD and BPD or death

	Odds ratio	95% CI	p-value
Variable associated with BPD (n=68)			
Requirement of surfactant	12.96	4.04-41.57	<0.001
Need for invasive respiratory support after birth	7.2	2.18-23.75	0.01
Variable associated with BPD or death (n=101)			
Requirement of surfactant	13.7	5.08-37.22	<0.001
Need for invasive respiratory support after birth	13.8	4.66-40.8	<0.001

BPD: Bronchopulmonary dysplasia, CI: Confidence interval

Discussion

BPD is the most prevalent morbidity of preterm birth despite considerable improvements in perinatal care and diverse neonatal care. BPD effects 10,000 to 15,000 infants annually in United States (1-3). In this retrospective, single-center cohort study the incidence of BPD was found to be 46%, and respiratory distress, requirement of surfactant and invasive ventilation were shown to be risk factors for the occurrence of BPD among ELBW infants.

Due to the interrelationship of many perinatal and neonatal factors, it is often difficult to isolate the exact risk factors for development of BPD. Various studies have identified male sex, degree of immaturity, and greater levels of respiratory support as important early predictors of BPD or death in ELGANs (7,9,16). In our study, both BPD and BPD or death occurred in infants with lower GA and BW regardless of gender. It was reported that the presence of RDS increases the development of BPD, while BPD may also develop without RDS (17). We found a significantly higher rate of RDS in the infants with BPD compared with the infants without BPD (81% vs 24%). Exogenous surfactant treatment is effective in the treatment of RDS, but it was not shown to decrease the incidence of BPD (8,14,18). The rate of the requirement of surfactant was approximately four-times higher in infants with BPD, and found to be a major risk factor for development BPD in our study.

MV has been a mainstay therapy in the care of preterm infants at risk for RDS due to premature lung development. It was reported by Neonatal Research Network that 89% of ELBW infants were treated with MV during the first day after. In our cohort, 69% of infants received invasive ventilation at first DOL. Although often life-saving, MV has poor effects by causing tissue injury and inflammation that contributes to BPD (19). The current best evidence shows that stabilization with CPAP, avoiding intubation decreases the risk of BPD and/or death in very low birth weight infants (20-23). In infants who are intubated, the duration of MV is a significant predictor of the development of BPD. In a large retrospective cohort study of ELBW infants, it was noted that the risk of developing BPD increased with the cumulative duration of MV, but it was not related to the number of ventilation courses (12). Robbins et al. (24) reported that the age at first extubating attempt correlated directly with endotracheal MV days and length of stay in a cohort of 224 infants born at <27 weeks' gestation. They also reported that an earlier extubating attempt is associated with lower incidence of BPD (24). In another retrospective study of 262 preterm infants born ≤28 weeks' gestation who were intubated in first DOL, it was noted that delayed extubating beyond the first 7-days was associated with an increased risk of BPD and BPD or death (25). Our study essentially reaffirmed the findings of the above studies, besides we found that invasive ventilation longer than 2.5 days is associated with an increased risk of BPD.

The early use of non-invasive ventilation was investigated as a means of preventing BPD. It was reported that infants who were intubated at birth had higher rates of BPD compared with those who received non-invasive ventilation for stabilization in the secondary analysis from the Caffeine for Apnea of Prematurity trial by DeMauro et al. (26). A recent meta-analysis which compares early use of CPAP to intubation and MV with or without surfactant demonstrated a reduction in the incidence of both BPD and BPD or death (27). Another meta-analysis demonstrated a decrease in BPD or death with using non-invasive ventilation to avoid MV in preterm infants born <30 weeks' gestation (28). In our study, we showed that the use of non-invasive respiratory support on the first DOL decreased the incidence of BPD and BPD or death.

BPD is also associated with higher rates of non-respiratory comorbidities, such as ROP and brain injury (4). The rate of ROP was higher in infants with BPD (26 vs 5%, p=0.018).

Study Limitations

There are some limitations of this study. The study includes the data of a single-center. All infants admitted to our NICU receive standardized and evidence-based treatment, but the number of included infants to this study was relatively small. Nevertheless, this study provides important conclusions for risk factors and especially for the duration of invasive MV for development of BPD.

Conclusion

In conclusion, requirement of surfactant therapy and need for invasive MV after birth were found to be major risk factors for the development of BPD and BPD or death. Respiratory support should be non-invasive initially after birth. If the infant is intubated, we recommend an attempt to extubate early within first 3-days after birth to prevent the development BPD and BPD or death.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ethics Committee of Ankara University Faculty of Medicine with number 18-1212-18.

Informed Consent: The study was a retrospective study.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Concept: E.O., Ö.E., Design: E.O., Ö.E., Analysis or Interpretation: B.A., S.A., Writing: E.O., Ö.E., B.A., S.A.

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