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The Effect of Early Neonatal Sepsis on Bronchopulmonary Dysplasia in Very Low Birth Weight Infants

Çok düşük doğum ağırlıklı bebeklerde Erken Neonatal Sepsisin Bronkopulmoner Displazi Üzerine Etkisi

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ÖZ

Amaç: Bronkopulmoner displazi (BPD), çok düşük doğum ağırlıklı bebeklerde en önemli morbiditelerden biridir. BPD multifaktöriyel bir hastalıktır ve patogenezinde inflamasyon önemli bir rol oynamaktadır. Bu çalışmadaki amacımız, preterm bebeklerde erken neonatal sepsis (ENS) varlığının BPD ve diğer preterm morbiditeleri üzerine etkisinin araştırılmasıdır.

Yöntem: Bu retrospektif çalışmaya, gebelik yaşı <30 hafta ve doğum ağırlığı <1500 g olan preterm bebekler dahil edildi. Yeni doğan yoğun bakım ünitemizde 2013-2016 yılları arasında izlenen bebeklerin kayıtları incelendi. ENS tanısı olanlar çalışma grubu olarak belirlenirken, diğer bebekler kontrol grubunu oluşturdu. Majör konjenital anomalisi, perinatal asfiksi olan ve verileri eksik olan bebekler çalışma dışı bırakıldı.

Bulgular: Çalışmamıza toplam 390 bebek dahil edildi. ENS ve kontrol grubunda gebelik yaşı 27,5±1,2 ve 27,6±1,2 hafta, p=0,44)ve doğum ağırlığı (1013±230 ve 1016±217 g,) istatistiksel olarak benzer saptandı. ENS grubunda, orta-ağır BPD (sırasıyla %14,6 ve %9,2, p=0,04) ve mekanik ventilatör gereksinimi istatistiksel olarak daha sık ancak postmenstrüel 36. haftada BPD olmadan sağ kalım (sırasıyla %63,1 ve %73,5, p=0,03) daha düşük oranda saptandı. Lazer tedavisi gereken prematüre retinopatisi ENS grubunda (%16,2 ve %9,6, p=0.03) anlamlı olarak daha sık iken, diğer preterm morbiditeleri açısından iki grup arasında fark saptanmadı. Çok değişkenli lojistik regresyon analizinde ENS'nin orta-ağır BPD gelişimi açısından bağımsız risk faktörü olduğu belirlendi (OR 1,89 % 95 CI 1,10-3,25, p=0,02).

Sonuç: ENS çok düşük doğum ağırlıklı bebeklerde orta-ağır BPD için bağımsız bir risk faktörüdür.

Anahtar kelimeler: Erken sepsis; bronkopulmoner displazi; prematürite; prematüre retinopatisi

ABSTRACT

Objective: Bronchopulmonary dysplasia (BPD) remains a critical morbidity in very low birth weight (VLBW) infants. The etiology is multifactorial, and inflammation plays an essential role in the pathogenesis. We aimed to investigate the effect of early neonatal sepsis (ENS) on BPD and other preterm morbidities in VLBW infants.

Materials and Methods: Preterm infants of <30 weeks of gestation and birth weight <1500 g were incorporated in this retrospective study. We reviewed the records of infants who admitted to the neonatal intensive care unit between 2013 and 2016. Those with ENS diagnosis were assigned to the study group, while the remaining constituted the control group. Babies with major congenital anomalies, perinatal asphyxia, and missing data were excluded from the study.

Results: This study included a total of 390 infants. The gestational ages (27.5±1.2 vs. 27.5±1.2 vs. 27.6±1.2 weeks) and birth weights (1013±230 vs. 1016±217 g, p=0.95) were statistically similar in the groups. Moderate-to-severe BPD (14.6% vs. 9.2% respectively, p=0.04) and requirement for invasive ventilation were more frequent, but survival without BPD at 36 weeks corrected (p=0.03) was lower in the ENS group. While llaser requiring retinopathy of prematurity ROP was significantly more common in the ENS group (16.2% vs. 9.6%, p=0.03), there was no difference between the groups regarding other preterm morbidities. In the multivariate logistic regression analysis, ENS was noted as an independent risk factor for moderate/severe BPD (OR 1.89 95 % CI 1.10-3.25, p=0.02).

Conclusion: ENS was demonstrated as an independent risk factor for moderate-severe BPD.

Keywords: Early sepsis; bronchopulmonary dysplasia; prematurity; retinopathy of prematurity

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INTRODUCTION

Early neonatal sepsis (ENS) remains a significant morbidity with an incidence of 10 per 1000 live births in preterm infants despite the widespread usage of antenatal antibiotic prophylaxis (1). The obstacle concerning ENS in preterm infants is the higher incidence of neonatal morbidity, particularly respiratory and neurological adverse outcomes, and mortality (1). The absence of a universal definition for neonatal sepsis and the variability in diagnostic criteria in the literature hampers the diagnostic process and treatment in neonates, particularly preterm babies (2). On the other hand, the time interval adopted for the diagnosis of ENS varies widely in the literature (3). A considerable percentage of the units put the diagnosis only by the presence of bacteremia, regardless of the clinical findings. Despite the widespread usage of noninvasive ventilation, minimally invasive surfactant implementation, and widespread antenatal steroid use, the incidence of bronchopulmonary dysplasia (BPD) remains stable. Besides the debate regarding the definition, over half of the very preterm infants receive a BPD diagnosis based on current criteria (4). Despite little data regarding the outcomes of very preterm babies with ENS, many etiological factors such as the type of pathogen, timing of infection, presence of chorioamnionitis, and fetal inflammatory response might affect the development and/or the severity of the disease (5). Exposure to bacteria and inflammation during the antenatal and/or postnatal period is known to disrupt alveolarization and causes fibrosis (6).

The relationship between infection and preterm mortality/morbidity has long been a topic of interest to researchers (1). Perinatal inflammation has been linked to BPD, retinopathy of prematurity (ROP), and brain lesions (6-8). Besides, a couple of studies have shown the constellation of preterm morbidities in clusters (9). ELGAN study revealed infection as a risk factor for ROP and BPD in infants < 28 weeks of age, while the diagnosis of sepsis was put by the presence of bacteremia without any clinical criteria (9). Along with variations regarding neonatal sepsis diagnostic criteria, the absence of a universally accepted diagnostic system hinders the comparison of the studies.

Studies have shown that postnatal infection/inflammation was associated with respiratory and neurological morbidity in preterm infants along with the controversy regarding intrauterine infection/inflammation and the BPD relationship (6,7). A couple of these studies investigated the link between neonatal sepsis and preterm morbidity, while others comprised only patients with culture-proven sepsis (10,11). We opted to search the effect of clinical and culture-proven ENS on BPD and other preterm morbidities in very-low birth weight (VLBW) infants.

MATERIALS AND METHODS

We conducted this retrospective cohort study in Zekai Tahir Burak Women's Health Education and Research Hospital between January 2013 and December 2016. Babies who were born alive at $250/^{7}$-$296/^{7}$weeks of gestation were included in the study. Exclusion criteria were major congenital/chromosomal anomalies, perinatal asphyxia, and lack of data.

We reviewed the obstetric and neonatal files. The obstetric and medical history of the mother, mode of delivery, and presence of intervention in the delivery room were recorded from the patient files. Surfactant requirement, BPD (mild-moderate-severe), survival without BPD at 36 weeks corrected, duration of invasive/noninvasive ventilation, patent ductus arteriosus (PDA), grade 3-4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), and the presence of ROP were noted.

All clinical and culture-proven ENS cases were included in the study. Clinical ENS was defined as the presence of clinical findings in keeping with sepsis within the first 72 hours of life, accompanied by elevated acute phase reactant but negative blood culture taken in the first three days. Culture-proven sepsis was defined as blood culture positivity beside clinical findings. While fungal sepsis was included in this analysis, viral infections were not incorporated into the study.

The classification of BPD was made based on the suggestion by Jobe EH and Bancalari E. at the 2001 National Institutes of Health Workshop (12). The definition of ROP was done according to the International Classification of Retinopathy of Prematurity 2 (ICROP-2) system (13). Papile classification was utilized for IVH staging (14). The diagnosis of hemodynamically significant PDA was made by echocardiography performed by a pediatric cardiologist.

The local ethics committee of our hospital approved the study. Verbal or written consent was obtained from the families.

Statistics

Analyzes were performed using SPSS version 21 (IBM SPSS Statistics, Chicago, IL, USA). Chi-square or Fisher exact test was used for the comparison of categorical variables. In the

case of continuous variables, the Student's t-test or Mann-Whitney U test was used for the comparison of groups. The comparison of the dependent groups was performed by the Wilcoxon test. p<0.05 was considered statistically significant.

RESULTS

We performed a retrospective analysis of a total of 390 patients. While 130 were diagnosed with ENS (study group), the remaining 260 constituted the control group. The gestational ages and birth weights were similar in the groups (Table 1). In the study group, 15 patients were diagnosed with culture-proven ENS. E. coli was detected in six, K. pneumoniae in five, and S. agalactiae in four patients. There was no statistically significant difference between the groups regarding demographic and maternal characteristics (Table 1).

Table 1. Demographic characteristics of the groups

	ENS group (n=130)	**Control group (n=260)**	***p***
Gestational age, weeks*	27.5±1.2	27.6±1.2	0.44
Birth weight, g*	1013±230	1016±217	0.95
Small for gestational age, n (%)	19 (14.6)	35 (13.5)	0.75
Male, n (%)	70 (53.8)	128 (49.2)	0.39
caesarean section, n (%)	110 (84.6)	202 (77.7)	0.10
APGAR ^{5}†	7 (6-8)	7 (6-8)	0.52
Multiple pregnancy, n (%)	27 (20.8)	52 (20)	0.85
Antenatal steroid, n (%)	92 (70.8)	171 (65.8)	0.32
Preeclampsia, n (%)	17 (13.1)	46 (17.7)	0.24

* mean±standard deviation †median, interquartile range (IQR)

The gestational weeks (27.5±1.2 vs. 27.6±1.2, p=0.44) and birth weights (1013±230 vs. 1016±217 g, p=0.95) were statistically similar in the groups. The relationship between ENS and preterm morbidities is demonstrated in Tables 2 and 3.

Table 2. Respiratory morbidity of the groups	**ENS group (n=130)**	**Control group (n=260)**	***p***
Requirement for surfactant, n (%)	95 (73.1)	166 (63.8)	0.06
Two doses of surfactant, n (%)	36 (27.7)	48 (18.5)	**0.03**
Mild bronchopulmonary dysplasia, n (%)	45 (34.6)	79 (30.49	0.10
Moderate-severe bronchopulmonary dysplasia, n (%)	19 (14.6)	24 (9.2)	**0.04**
Survival without bronchopulmonary dysplasia at 36 weeks, n (%)	82 (63.1)	191 (73.5)	**0.03**
Duration of noninvasive ventilation, days†	5 (2-12.5)	5 (2-13)	0.81
Duration of invasive ventilation, days†	2 (0-6)	1 (0-4)	**0.03**
Duration of supplemental O2, days†	12.5 (2-24.5)	11 (4-24)	0.75
Air leak, n (%)	2 (1.5)	3 (1.2)	0.74

†median, interquartilerange (IQR)

Table 3. Other preterm morbidities and clinical features of the groups

	ENS group (n=130)	Control group (n=260)	*p*
Proven late-onset sepsis, n (%)	35 (26.9)	61 (23.5)	0.45
Number of proven late-onset sepsis episodes†	0 (0-1)	0 (0-0)	0.59
Patent ductus arteriosus, n (%)	56 (43.1)	105 (40.4)	0.61
Grade III-IV Intraventricular hemorrhage, n (%)	21 (16.2)	26 (10)	0.12
Periventricular leukomalacia, n (%)	14 (10.8)	16 (6.2)	0.09
Necrotizing enterocolitis grade ≥IIb, n (%)	1 (0.8)	7 (2.7)	0.27
Spontaneous intestinal perforation, n (%)	2 (1.5)	3 (1.2)	1
Retinopathy of prematurity requiring laser treatment, n (%)	21 (16.2)	25 (9.6)	**0.03**
Mortality, n (%)	28 (21.5)	39 (15)	0.10
Length of hospital stay, days†	64 (52-839)	66 (51-81)	0.70
Postmenstrual age at discharge, weeks*	37.4±2.7	37.2±2.4	0.82

* mean±standard deviation †median, interquartile range (IQR)

Although the requirement for surfactant was statistically similar in the groups (p=0.06), the need for ≥two doses of surfactant was higher in the ENS group (p=0.03). The incidence of moderate-severe BPD (p=0.04) was higher, and the duration of invasive ventilation (p=0.03) was significantly longer in the ENS group. Besides, the study group was less likely to survive without BPD at postmenstrual 36 weeks (p=0.03). While ROP requiring laser therapy was significantly more common in the ENS group (p=0.03), no difference was found between the groups concerning other preterm morbidities. In the multivariate logistic regression analysis, ENS was noted as an independent risk factor for moderate/severe BPD (OR 1.89 95 % CI 1.10-3.25, p=0.02).

DİSCUSSION

We revealed a longer duration of invasive ventilation, and higher incidence of ROP requiring laser treatment, and lower survival without BPD at 36 weeks corrected in VLBW infants who experienced ENS.

Klinger et al. investigated the outcomes of VLBW infants with ENS in a wide-scale prospective observational study including 15,839 infants from 28 neonatal intensive care units (15). The incidence of severe ROP and BPD was noted to be higher in extremely low birth weight infants with ENS, like our study (15). Although no data was available regarding the duration of mechanical ventilation, researchers hypothesized that the higher BPD risk was most likely related to prolonged exposure to assisted ventilation. ROP and unfavorable neurological outcomes were assumed to be associated with the inflammatory response. On the other hand, only babies with culture-proven ENS were incorporated in that trial as opposed to our study.

Neonatal sepsis was shown to be a strong risk factor for BPD in a single-center, large series from Australia that comprised 798 infants <30 weeks (16). Patients with blood culture positivity before the 36 weeks corrected were included in the study with the diagnosis of sepsis. Unlike the literature and our study, bacterial growth in the blood cultures taken before the 48th hour of life was defined as ENS (16). However, a separate analysis was not performed based on the timing of onset. Besides, the definition of sepsis as the documentation of bacteremia without taking clinical findings into account was the limitation of the study. A significant percentage of these growths might be contamination or bacteremia that was not accompanied by an illness state.

Ohlin et al. showed that 66% of the entire cohort had at least one episode of sepsis in a national prospective study comprising 497 infants of <27 weeks' gestation (17). While proven sepsis was shown as a risk factor for severe BPD, there was no significant association between clinical sepsis and BPD. The strength of this study was the large sample size with the comparison of the groups as clinical and proven sepsis. The difference between the groups regarding BPD might be indicating a more severe disease pattern in case of culture growth in the newborn. One should assess the results with caution given that the study incorporated only live babies.

ELGAN study showed a relationship between early/late bacteremia and ROP in 1223 infants <28 weeks of gestation (9). However, late bacteremia minimally increased the risk of

BPD, not early bacteremia in that study. On the other hand, the authors revealed the coexistence of severe ROP and BPD in extremely low birth weight infants (9). Besides, the definition of early bacteremia was made as culture growth in the first week of life, while the authors defined late bacteremia as growth in blood cultures taken between postnatal weeks 2-4. That classification is not in keeping with the neonatal sepsis guidelines. In addition , clinical findings were not considered in putting the diagnosis of sepsis. Even if a link was demonstrated between severe ROP and ENS in our study, it remains compelling to compare our results with the ELGAN study due to the diversity in the terminology.

There are a couple of strengths and limitations of our study. Both clinical and culture-proven ENS cases constituted the study group and were compared with the infants who never experienced an ENS episode. The results should be evaluated with caution given the predominance of clinical sepsis cases in the study group. A subgroup comparison could not be performed because of the insufficient number of culture-proven patients. However, the exclusion of the patients with contamination was an important strength of our study. Besides, similar rates of late-onset sepsis presumably prevented any confounding effect on the results.

To conclude, ENS was shown as an independent risk factor for moderate-severe BPD in VLBW infants. Further large-scale prospective studies are warranted to reveal further impact of ENS on neonatal morbidity.

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