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Severe Intraventricular Hemorrhage is Associated with Lung Injury in Preterm Infants on Mechanical Ventilation

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Abstract

Background: The aim of this study was to better understand the relationship between intraventricular hemorrhage and the risk of development of early lung disease in extremely low birth weight infants. We hypothesize that infants with severe intraventricular hemorrhage have higher respiratory severity scores than infants with mild/no intraventricular hemorrhage within the first 7 days of life.

Methods: This was a single center retrospective study conducted on subjects born between 01/01/2018 and 06/30/2021 at the University of Kentucky Children's Hospital NICU. We enrolled preterm infants with gestational age of less than 30 weeks and birth weight of less than 1000 grams who were placed on mechanical ventilation on admission.

Results: We found a clinically significant increasing trend of respiratory severity scores within the first week of life in the group of infants with severe intraventricular hemorrhage.

Conclusion: This study is first to show that severe intraventricular hemorrhage is associated with higher respiratory severity scores predicting early lung injury in the extremely low birth weight infants placed on a mechanical ventilator within the first 7 days of life.

Keywords: Intraventricular hemorrhage; Respiratory severity score; Preterm infant; Lung disease

Introduction

The pathogenesis of Intraventricular Hemorrhage (IVH) in preterm neonates is multifactorial. It is influenced by inflammation during the prenatal, perinatal, and postnatal periods [1-3]. Factors such as chorioamnionitis, postnatal resuscitation, Early Onset Sepsis (EOS), Respiratory Distress Syndrome (RDS), and mechanical ventilation all play a role in the risk of development of IVH in premature neonates [2-5]. An association between mechanical ventilation and IVH has been previously described, focusing on mechanical ventilation as a contributing factor to the development of IVH [6]. Mechanical ventilation impedes venous return due to positive intrathoracic pressure, hence impacting cardiac output. This mechanism may contribute to the development of brain injury in Extremely Low Birth Weight (ELBW) neonates [6]. The incidence of severe IVH increases threefold in ELBW infants who undergo early mechanical ventilation [6]. However, no clinical studies so far have investigated how brain injury may exacerbate lung injury in preterm neonates. Observational studies in adults and experimental animal studies have demonstrated how respiratory dysfunction may follow brain injury [7-9]. For instance, Kitamura et al reported that half of patients admitted

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for subarachnoid hemorrhage (SAH) developed systemic inflammatory response syndrome and acute lung injury [7]. Hypoxic brain damage in newborn piglets has been reported to lead to inflammatory lung damage, placing them at higher ventilatory needs [9].

Multiple studies report that elevated Respiratory Severity Scores (RSSs) predict chronic lung disease in the premature neonates [10-11]. RSS is a tool to monitor the severity of respiratory failure, defined as a product of mean airway pressure (MAP) multiplied by fractional inspiration of oxygen (FiO_2) [10]. RSS ≥ 3.0 at postnatal day 14 and RSS ≥ 3.6 at postnatal day 21 in intubated infants is predictive of severe BPD or death [11]. The aim of this study was to investigate the relationship between IVH and lung injury in the ELBW neonates placed on high frequency jet ventilator (HFJV) within the first week of life.

Methods

Study design and subjects

This was a single - center retrospective cohort study, we enrolled preterm infants with a gestational age of less than 30 weeks of gestation, and birth weight of less than 1000 grams who were admitted to the neonatal intensive care unit (NICU) at Kentucky Children's Hospital between 01/01/2018 and 06/30/2021. Approval for this study was obtained from the University of Kentucky Institutional Review Board. Infants born less than 30 weeks gestation are at the greatest risk for the development of IVH, and all infants below this gestational age have routine screening head ultrasounds per our unit clinical practice guidelines. Upon admission to the NICU from the delivery room, infants were placed on a HFJV. The exclusion criteria were as follows: 1) patients with major congenital anomalies; 2) patients who were on mechanical ventilation for less than 48 hours of life; 3) patients who died within 48 hours.

Using the Papile's classification mild IVH was defined as Grade I and Grade II, while severe IVH was defined as Grade III and Grade IV. According to this classification, 72% had mild/no IVH while 28% had severe IVH. For assessing severity of IVH, we used images from head ultrasounds obtained on day 3 and day 7 of life, which were reported by a pediatric radiologist in our institution.

Statistical analysis

Categorical variables were analyzed using Pearson's chi-square or Fisher's exact test as appropriate. Continuous variables were analyzed utilizing independent samples t-tests or 3 independent samples difference of medians as appropriate. Parametric data were expressed as mean ± standard deviation, non-parametric data were expressed as median and interquartile range. Categorical data were expressed with counts and percentages. Bivariate analysis was used to evaluate individual variables including demographics, and infant clinical characteristics associated with IVH. Significant variables found in the bivariate analysis were further analyzed using a multivariate logistic regression analysis with a backwards elimination selection process. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 27 software package.

Results

Patient demographics and clinical outcomes

Of the 258 neonates born with a birth weight of less than 1000 grams during study period, 135 infants met the inclusion criteria.

The demographic and clinical characteristics of subjects with and without severe IVH are shown in Table 1. Infants who had severe IVH had significantly lower gestational ages [(24.3 0 ± 1.0 vs. 26.0 ± 1.8); p<0.001], birth weights [(667 ± 138 vs. 732 ± 147); p=0.021] and were delivered by vaginally (63% vs. 82%, p=0.018). There was no difference regarding intrauterine growth restriction (IUGR) status (17% vs. 8%; p=0.188), male sex (53% vs. 42%; p=0.274), race (p=0.517), Apgar scores at 1 and 5 minutes (p=0.758 and p=0.440, respectively) between the mild/no IVH and severe IVH groups. As far as maternal characteristics are concerned, there was no difference between maternal age in mild/no IVH vs severe IVH groups [(29 ± 6.5 vs. 27 ± 6; p=0.142), median (IQR) rupture of membranes (ROM) [71 (0-4) vs. 50 (0-18) (p=0.415)], chorioamnionitis (16% vs. 26%; p=0.193), gestational DM (11% vs. 8%; p=0.757) and intrauterine drug exposure (8% vs. 5%; p=0.725). Administration of postnatal steroids was similar between two groups (39% vs. 34%; p=0.633). 80% of infants who had mild /no IVH had mothers who received a full course of prenatal steroids versus 63% within the severe IVH group (p=0.036). 41% of mothers of infants with mild/no IVH had a history of hypertension/ preeclampsia vs. 21% of mothers within the severe IVH group (p=0.028).

Clinical courses comparison between two groups in the first week of life is illustrated in Table 2. Neonates with severe IVH were more likely to be placed on single (21% vs. 6%; p=0.011) or multiple pressors (37% vs. 12%; p=0.001), receive blood transfusion (p<0.001) within first 7 days of life. Both groups showed no difference in their hematocrit on admission (p=0.066), temperature on admission (p=0.899), incidence of EOS (p=0.901), or incidence of pulmonary hemorrhage (p=0.091).

The duration of mechanical ventilation did not differ between the groups as shown in Table 3. Median (IQR) number of days on a ventilator spent by the severe IVH group was 45 (27-75) and by the mild/no IVH group was 35 (9-60).

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Table 1: Demographic and clinical characteristics of subjects with and without severe IVH.

Variable	IVH Mild/None (n=97)	IVH Severe (n=38)	P Value
Infant			
Gestational Age, mean (SD)	26.0 (1.8)	24.3 (1.0)	<0.001
Birth Weight, mean (SD), g	732 (147)	667 (138)	0.021
IUGR, n (%)	17 (17)	3 (8)	0.188
Cesarean Section, n (%)	79 (82)	24 (63)	0.018
Male Sex, n (%)	51 (53)	16 (42)	0.274
Race, n (%)			
Caucasian	87 (90)	32 (85)	0.517
African American	7 (7)	5 (13)	
Hispanic	3 (3)	1 (3)	
Apgar score at 1 min, median (IQR)	2 (5-1)	2 (4-1)	0.758
Apgar score at 5 min, median (IQR)	6 (7-3)	5 (7-4)	0.44
Late Onset Sepsis, n (%)	22 (23)	14 (56)	0.019
Postnatal steroids, n (%)	36 (39)	11 (34)	0.633
Mother			
Age at Delivery, mean (SD), y	29 (6.5)	27 (6)	0.142
ROM, median (IQR), hours	71 (4-0)	50 (18-0)	0.415
Use of Antenatal Steroids, n (%)	78 (80)	24 (63)	0.036
Chorioamnionitis, n (%)	16 (16)	10 (26)	0.193
Hypertension/Preeclampsia, n (%)	40 (41)	8 (21)	0.028
Gestational DM, n (%)	11 (11)	3 (8)	0.757
Intrauterine Drug Exposure, n (%)	8 (8)	2 (5)	0.725

Number of infants who survived with severe BPD as well as ventilatory support was similar between the groups (17.4% in the severe IVH group vs. 7.8% in the mild/none IVH group; p=0.230). We noted that infants with mild/no IVH were more likely to be on CPAP at 36 weeks of CGA (56 % vs. 30% in the severe IVH group). Infants with severe IVH were more likely to be on a ventilator at 36 weeks of CGA (17% vs. 8% in the mild/no IVH group). Ventilatory support at discharge did not differ between the groups (p=0.492). Higher mortality was reported in neonates with severe IVH before (21% vs. 1%; p<0.001) and after 7 days of life (26% vs. 5.2%; p<0.001).

The results of logistic model for the overall study population showed that infants with severe IVH were more likely to be placed on single pressor (OR=6.7, 95% CI [1.9, 22.9], p=0.003) or on multiple pressors (OR=7.7, CI [2.8, 21.8], p=<0.001) in the first 7 days of life. In addition, infants of mothers who received antenatal steroids were more likely to have mild/no IVH (OR= 0.3, CI [0.1, 0.7], p=0.011).

Relationship between IVH and RSS

The comparison of RSS values at postnatal days 1 through 7 between the two groups are shown in Table 4. The relationship between RSS and severe IVH was found to be clinically significant especially at days of life: 2, 3, 4, 5, 6, 7. First week of life median (IQR) RSS within the group with severe IVH was also significantly higher than in the group with mild/no IVH [3.6 (2.7-4.1) vs. 2.3 (2.0-3.1)] (p<0.001).

Table 2: Clinical courses comparison between two groups in the first week of life.

	IVH Mild or None	IVH Severe	P Value
Hematocrit, median (IQR)	43 (35-46)	36 (32-43)	0.066
Temp on admission, median (IQR)	98 (97-98)	98 (97-98)	0.899
Pressors, n (%)	20 (21)	22 (58)	
Single pressor	6 (6)	8 (21)	0.011
Multiple pressors	12 (12)	14 (37)	0.001
Early Onset Sepsis, n (%)	12 (12)	5 (13)	0.901
Pulmonary Hemorrhage, n (%)	8 (8)	7 (18)	0.091
Transfusions, median (IQR)	2 (3.5-1)	4 (6-3)	<0.001
Death, n (%)	1(1)	8 (21)	<0.001

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Table 3: Respiratory outcomes

	IVH Mild or None	IVH Severe	P Value
DOL extubated, median (IQR)	35 (60-9)	45 (75-27)	0.134
Survivors with severe BPD, n (%)	7 (7.8)	4 (17.4)	0.23
Support at 36 weeks, n (%) RA NC CPAP NIV VENT	 16 (18) 9 (10) 50 (5.6) 8 (9) 7 (8)	 6 (26) 3 (13) 7 (30) 3 (13) 4 (17)	0.19
Support at Discharge, n (%) RA NC VENT	 36 (40) 51 (56) 4 (4)	 10 (50) 10 (50) 0 (0)	0.492
Death after 7 days of life, n (%)	5 (5.2)	10 (26)	<0.001

Table 4: Comparison of RSS values at postnatal days 1 through 7 between the two groups.

	RSS Day 1	RSS Day 2	RSS Day 3	RSS Day 4	RSS Day 5	RSS Day 6	RSS Day 7
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
IVH Mild or None	2.0 (1.6-2.4)	2.0 (1.6-2.6)	2.2 (1.8-2.9)	2.2 (1.9-3.1)	2.4 (2.0-3.2)	2.5 (2.1-3.5)	2.6 (2.1-3.6)
IVH Severe	2.2 (1.8-3.6)	2.5 (2.1-3.4)	3.0 (2.4-4.5)	3.3 (2.5-4.1)	3.3 (2.5-4.2)	3.2 (2.5-4.7)	3.4 (2.8-4.9)
P Value	0.215	0.005	<0.001	<0.001	0.002	0.026	0.009

Discussion

We performed this study to investigate if severe IVH is associated with worsening lung disease in ELBW infants. In this cohort, neonates were primarily intubated in the delivery room and surfactant was administered as early as possible [12-14]. The standard of care in our unit is to use HFJV on admission for ELBW infants. We demonstrated that ELBW infants with severe IVH in contrast to those with mild/no IVH, have a significantly increasing trend of RSSs within the first seven days of life. Increasing trend of RSSs in the group of infants with severe IVH can be explained by the brain - lung crosstalk. After IVH occurs, erythrocytes lyse and their toxic components are released into the ventricular system and induce brain damage [15]. Hemoglobin was previously described as having major cytotoxic effects on periventricular brain damage [16]. Lysed hemoglobin can release tumor necrosis factor- α (TNF-α) in the CSF [17]. Evidence suggests that after the brain injury, other proinflammatory cytokines and microglia are activated and there is massive leukocyte infiltration into the brain [15]. Due to the increased blood brain barrier permeability, proinflammatory mediators can later be released into systemic circulation and lead to multiorgan dysfunction [18]. We speculate that after severe IVH occurs, these proinflammatory cytokines are released into the systemic circulation and in the end affect extracerebral organs in a neonate. Infants who have developed severe IVH are therefore at increased risk of lung injury and requirement of higher RSSs as illustrated in our study.

The concept of extracerebral organ dysfunctions after brain injury was previously described in adult and animal studies [7,8,19]. Brain injury can make the lung more vulnerable to injury and ischemia-reperfusion insults, eventually leading to its failure [18]. There is increasing evidence that in the adult population subarachnoid hemorrhage (SAH) can be followed by non-neurological complications such as pulmonary edema, cardiac arrhythmia, renal and hepatic dysfunctions [19]. These non-neurological complications are unfortunately linked to poorer prognosis in this patient population [19]. Similarly, Veeravagu et al. [20] found that patients with SAH are at increased risk for developing acute respiratory distress syndrome (ARDS) and therefore at risk for poorer prognosis [20]. Damaged brains might be an important site

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of cytokine production and distribution as described in an experimental animal model by Arruza and colleagues [9]. They demonstrated that hypoxic-ischemic insult of the brain resulted in increased ventilatory needs of newborn piglets suggesting signs of pulmonary dysfunction following brain injury[9]. Another experimental animal model illustrated that ICAM-1 and tissue factors are elevated in both brain and lung tissues following experimental brain injury in rats [21].

Multiple prenatal and postnatal characteristics can affect development of IVH. Antenatal steroids use for example were found to be associated with reduction in incidence of any grade of IVH and reduction in incidence of severe IVH in preterm infants of less than 29 weeks of gestation [12]. In our study, maternal antenatal steroids exposure use was significantly different between severe IVH and mild/no IVH group. Infants of mothers who had antenatal steroids were more likely to have mild/no IVH and interestingly mothers of infants with mild/no IVH had a history of hypertension/ preeclampsia. Protective effect of maternal hypertension/ preeclampsia against development of IVH has been described in the literature before. Perlman et al. [13] reported a significantly lower incidence of IVH in infants born to mothers with pregnancy - induced hypertension.

We also demonstrated that within the group with severe IVH, infants were more likely to be placed on single or multiple pressors and have a higher number of transfusions within the first seven days of life. There are multiple reasons for hypotension in ELBW infants: lack of antenatal steroids, perinatal blood loss, sepsis, hemodynamically significant PDA, impaired venous return caused by high positive intrathoracic pressure (PEEP) [14]. There is evidence to support the association between systemic hypotension and IVH [14]. It is not surprising that infants with severe IVH in our study were previously placed on single or multiple pressors. In our logistic regression model, single pressor (OR=6.7, 95% CI [1.9, 22.9], p= 0.003) and multiple pressors (OR=7.7, CI [2.8, 21.8], p=<0.001) in the first 7 days of life were found to be associated with severe IVH.

To our knowledge this is the first study investigating the effects of IVH on lung disease in the ELBW infants. Injury to the surrounding tissue that occurs after severe IVH triggers an inflammatory pathway leading to systemic release of proinflammatory cytokines and eventual injury to the lungs. There is overwhelming evidence that, if survived, infants with severe IVH are at higher risk for developmental delay, cerebral palsy, and deafness [1,3,22]. In this study we learned that severe IVH also predisposes ELBW infants to lung injury and an increasing trend of RSSs. Investigating the proinflammatory cascade markers released after IVH should become the focus of further clinical research. We believe that better identification of relationships of brain injury and mechanical ventilation in ELBW infants can provide opportunities for novel therapies that could prevent development of chronic lung disease in this population.

There are some limitations to this study. This analysis was retrospective in nature and based on experiences within a single center. We relied on the data extracted from the medical records. We studied infants only placed on HFJV. In addition, we relied on head ultrasound findings from DOL 3 and DOL 7, perhaps more frequent head ultrasounds would better define the timeline of IVH and RSS.

Conclusion

We have demonstrated that severe IVH may be a risk factor for the development of early lung disease in the ELBW neonates placed on mechanical ventilation. We speculate that after severe IVH, inflammatory markers are released into the systemic circulation, affecting extracerebral organs particularly leading to injury of the lungs. The injury of the lungs is explained by the increasing trend of RSSs within the first week of life. The relationship between IVH and early lung disease in the ELBW neonates was not discussed previously, hence a large prospective study is needed to study this finding further. If the inflammatory markers and their receptors are identified early, lung disease in the population of neonates with severe IVH could be prevented.

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