The Prognosis of Refractory Hypotension and Severe Intraventricular Hemorrhage in Very Low Birth Weight Infants

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Research

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Abstract

Background: The increased survival rate among very low birth weight infants has resulted in a higher risk for developing neurocomplications such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and adverse neurodevelopmental outcomes.

Purpose: We examined refractory hypotension experienced within a week of life in association with severe IVH (grades 3-4) among very low birth weight infants (VLBWIs).

Method: Between Jan 2014 and Dec 2017, the clinical data of 191 VLBWIs admitted were retrospectively reviewed. Of a total **of** 191 VLBWIs, 71.2% (136/191) had IVH, and 28.7% (55/191) had severe IVH.

Results: The VLBWI with severe IVH group (grade 3-4) presented with a significantly lower gestational age along with higher use of postnatal hydrocortisone for refractory hypotension. Resuscitation at delivery, pulmonary hemorrhage, neonatal seizure, and periventricular leukomalacia (PVL) were significantly more frequent in the severe IVH group ($p<0.05$). Higher mortality occurred in the VLBWI with severe IVH group ($p<0.001$). The multivariable logistic regression analysis consistently showed that refractory hypotension within a week of life and neonatal seizures were significantly associated with severe IVH. Those in the severe IVH and refractory hypotension groups had significantly lower composite cognitive, language, motor, and Bayley Scales of Infant and Toddler Development III scores at corrected 18 months.

Those in the severe IVH and refractory hypotension groups showed significant developmental delay.

Conclusion: Refractory hypotension within a week of life and seizures were consistently associated with severe IVH. VLBWI who experienced refractory hypotension within a week of life may indicate a more vulnerable perinatal settings with a higher risk for developmental delay.

Introduction

Progressive advances in neonatal practice along with antenatal and postnatal care have led to the increased survival rate of very low birth weight infants (VLBWIs). The increased survival rate in this population has resulted in a higher risk for developing neurocomplications such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and adverse neurodevelopmental outcomes. Neurological sequelae are found in approximately 50–75% of preterm survivors with severe IVH, and the finding of IVH invokes considerable anxiety about long-term sequelae when even survivors with mild grades of IVH develop physical impairments, such as cerebral palsy; as such, it remains a significant public health concern worldwide.[1] Prior studies have shown that IVH is well known to be associated with a lower gestational age and birth weight, while low Apgar score and male sex were not consistently associated with severe IVH. [2–3] After birth, known as risk factors for IVH include the uncontrolled use of oxygen therapy[2] in addition to frequent apnea events, sepsis, a history of surfactant treatment, and multiple transfusions. [3] Along with these risk factors, refractory hypotension is a common problem in the very premature infant population, with an estimated incidence of 20–45% [4], and there is an association

with IVH. [5] Refractory hypotension can diminish CO_2 reactivity in the brain due to vasodilated cerebral vessels, which can eventually decrease cerebral blood flow. The immaturity of the germinal matrix as well as fluctuations in cerebral blood flow with pressure changes can also affect premature infants' vulnerable cerebral blood flow. [6]

The goal of this retrospective chart review was to explore the risk factors for IVH, especially those who experienced refractory hypotension within a week of life in VLBWI. In our study, we hypothesized that infants who experienced refractory hypotension might be at risk for severe IVH and may indicate a more vulnerable perinatal settings with a higher risk for neuro-developmental delay.

Methods

Design and sample

We retrospectively analyzed the medical records of 191 VLBWIs admitted at Seoul St. Mary's Hospital between Jan 2014 and Dec 2017. Our study included VLBWIs born with birth weight < 1500 g or gestational age < 32 weeks at birth. Infants with chromosomal anomalies were excluded for confounding risk factors for IVH. The clinical risk factors influencing the development of IVH were analyzed. Brain sonogram was performed within a week of life for IVH screening among VLBWIs. For infants experiencing systemic hypotension, dopamine infusion was started at a rate of 5 μg/kg/min and increased by 2.5 μg/kg/min until an adequate mean blood pressure was achieved after fluid bolus challenges. If 10 μg/kg/min dopamine failed, dobutamine (10 μg/kg/min) was added. If dopamine and dobutamine treatment failed, hydrocortisone was added at a dose of 5 mg/kg/day IV, divided into three doses at 8-hour intervals.

Patients were evaluated for neurodevelopmental outcomes at corrected 18 months based on the Bayley Scales of Infant and Toddler Development III. The study was approved by the Ethics Committee of Seoul St. Mary's Hospital. Informed consent was waived for this study because it was a retrospective chart review, and all methods were performed in accordance with the relevant guidelines and regulations by the Ethics Committee of Seoul St. Mary's Hospital.

Definitions

Systemic hypotension in very low birth weight infants was defined as a mean blood pressure measured noninvasively as below the 3rd percentile for gestational age or below 30 mmHg [7]with decreased urine output > 12 hours. Refractory hypotension was defined when combination dopamine (10 μg/kg/min) and dobutamine (10 μg/kg/min) treatment failed and hydrocortisone (5 mg/kg/day IV, divided into three doses at 8-hour intervals) was needed for refractory hypotension. Pulmonary hemorrhage was defined as massive pulmonary hemorrhage, which affects vital signs as manifested by cardiovascular collapse or acute respiratory failure. Pulmonary hypertension was defined by the need to use nitric oxide or sildenafil or ≤ 1 week of life. Bronchopulmonary dysplasia (BPD) was diagnosed if oxygen use exceeding 0.21% was still needed at a corrected gestational age of 36 weeks.

Seizures were clinically diagnosed by experienced neonatology or neurologist staff as paroxysmal alterations in motor function and occasional autonomic function; this included clonic, tonic, and “subtle” seizure manifestations [Volpe JJ]. Necrotizing enterocolitis (NEC) was defined as grade II or higher using Bell’s classification. IVH > grade II was defined as active bleeding in the ventricles, and the grade designation was based on Drs. Papile and Levene’s classification criteria.[8] At the corrected age of 18 months, patients were considered at risk if scores were > 2 SDs below the test mean (scores of < 70). The abnormal neurodevelopmental outcome was defined when composite scores of < 70 in the areas of cognitive, language, or motor were found.

Statistical analysis

Continuous variables were compared using Student’s t-test and are expressed as the mean ± standard deviation. Discrete variables were compared using a $\chi 2$ test or Fisher’s exact test and are expressed as percentages. All the analyses were two-tailed, and clinical significance was defined as a p value less than 0.05. To identify any confounding risk factors for IVH, we used a multivariate logistic regression model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using both a multivariate statistical model that included the following predictors related to severe IVH and a stepwise logistic regression analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 15.0 (SPSS-PC Inc., Chicago, IL, USA).

Results

Of the 191 VLBWIs who were admitted to the neonatal intensive care unit between January 2014 and December 2017, 71.2% (136/191) of VLBWIs had IVH, and 28.7% (55/191) had no IVH. Table 1 compares the clinical characteristics of VLBWI without and with IVH; VLBWI with IVH had a significantly lower gestational age (27.54 ± 2.37 weeks vs 28.58 ± 2.75 weeks, $p < 0.009$) and RDS (129 (94.9%) vs 47 (85.5%), $p = 0.029$). With regard to morbidities, infants who developed IVH had significantly more neonatal seizures, sepsis, packed red blood cell (PRC) transfusions, bronchopulmonary disease (BPD) ≥ moderate, and PVL. Additionally, VLBWI with IVH had longer duration of total parenteral nutrition (TPN), duration of mechanical ventilation, and hospital stays ($p < 0.001$) than those without IVH. The hospital mortality rate was significantly different between the two groups.

Table 2 shows the higher severity of IVH characteristics among the VLBWIs with IVH (n = 136). The severe IVH group (> IVH grade II) exhibited a significantly lower gestational age (26.94 ± 2.47 weeks vs 27.94 ± 2.23 weeks, $p = 0.016$) than those with ≤ IVH grade II. Early hydrocortisone use was significantly higher in the severe IVH group. Resuscitation at delivery, pulmonary hemorrhage, neonatal seizure, and PVL were significantly more frequent in the severe IVH group ($p < 0.05$). Higher mortality occurred in the VLBWI with severe IVH group ($p < 0.001$). To explore the influence of any possible confounding factors on IVH and severe IVH in VLBWI, we performed a multivariable logistic regression analysis to identify any confounding factors related to IVH severity. Table 3 provides the risks for severe IVH (those with grades 3 and 4 (n = 55)) in a logistic regression analysis. We included gestational age, early hydrocortisone use for

refractory hypotension, pulmonary hemorrhage, and neonatal seizure in a multiple logistic regression analysis.

Because the other significant variables in Tables 1 and 2 usually occur after IVH incidence, they were not included in this analysis to observe as risk factors.

Refractory hypotension and seizures were consistently associated with severe IVH.

At the corrected age of 18 months, the VLBWI who had IVH (n = 136) completed the cognitive, language, and motor components of the Bayley Scales of Infant and Toddler Development III. Those with a history of severe IVH (grade 3–4) had significantly lower composite scores for all five areas – cognitive, language, motor, socioemotional, and adaptive behavior on the Bayley Scales of Infant and Toddler Development III (Table 4). In addition, the severe IVH group was at significantly high risk of neurodevelopmental outcomes at corrected 18 months, defined as a score > 2 SDs below the test mean (scores of < 70) (Table 4). Additionally, those experiencing refractory hypotension within a week of life had significantly lower composite scores for all three areas – cognitive, language, and motor – of the Bayley Scales of Infant and Toddler Development III (Table 5). They were also at high risk of neurodevelopmental delay, defined as a score > 2 SDs below the test mean (scores of < 70) (Table 5).

Discussion

In our study of VLBWI, we observed a 28.7% incidence of IVH among 191 very preterm infants, which was higher than the reported severe IVH incidence in the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network study in 2016, which was only 7.5%.[9] However, the mean gestational age in our study group was 27–28 weeks of age, weighing 1-1.1 kg in our VLBWI. A prior study investigating the IVH prevalence in premature Israeli infants according to weight and gestational age similarly reports IVH incidence of 20.9% [6], which was similar to our IVH rate of 28.7%. Among the multifactorial pathogenetic risks for IVH, abnormalities of the hemodynamic systems certainly play a role. We found that VLBWIs experiencing refractory hypotension within the first week of life who ultimately needed hydrocortisone to maintain appropriate blood pressure were at high risk for severe IVH (stages 3–4). Refractory hypotension can be a risk factor in the very preterm population, with an estimated incidence of 20–45% [10,] which is associated with IVH.[5]

Until the early 2000s, the postnatal steroid dexamethasone was used widely as clinical trials reported that dexamethasone reduced the risk of death or BPD in VLBWI; however, this benefit was outweighed by a possible increased risk of neurodevelopmental impairment.[11–13] While many randomized and control trials (RCTs) have also shown adverse neurodevelopmental outcomes after postnatal dexamethasone treatment for BPD, no multicenter RCT studies have demonstrated adverse effects on the long-term outcomes after hydrocortisone therapy.[14] This is because dexamethasone is 40 to 50 times more potent than hydrocortisone and longer- acting at 18 to 24 hours. [15] Hydrocortisone targets both glucocorticoid

and mineralocorticoid receptors, which may cause a less harmful effect on neurodevelopmental outcomes.[15]

The more severe hospital morbidities in the VLBWI group exposed to early hydrocortisone use in our study are directly related to increased severity of illness in VLBWI, especially when it occurred in the first 72 hours of life, as reported by Jonathan et al.[16] Similar to our study, refractory hypotension is reported to be associated with severe IVH, poor long-term neurodevelopment (permanent neurological injuries/deficits or cerebral palsy), and even death.[17–18] Our study also reported higher mortality in the severe IVH group (34.5%) and 38 (69.1%) VLBWIs in the severe IVH group. Overall, VLBWI experiencing refractory hypotension within the first week of life indicates hemodynamic instability and changes in cerebral blood flow, which increases the incidence of severe IVH.

Some studies have highlighted the negative effects of vasopressors in compromising cerebral autoregulation.[19] The vasoconstrictive effects of inotropic drugs could worsen the hypoxia-hypoperfusion status of the periventricular areas of the immature brain and result in glutamate- and free radical-induced damage to preoligodendrocytes, which are the precursors of oligodendrocytes that eventually form the white matter.[20] In fact, studies reported that the use of inotropes was associated with increased severe IVH in infants born before 32 weeks gestation.[21–22] This may be because hemodynamic instability and changes in cerebral blood flow are increased risks of IVH.[23]

Infants with refractory hypotension experienced mostly adrenal insufficiency, shock or RDS, demonstrating the importance of the severity of illness within a week of life and possibly suggesting a causal relationship with severe IVH. In our study, our center only used hydrocortisone as an alternative to dexamethasone to minimize the negative effect on neurodevelopmental outcomes. Since hydrocortisone targets both glucocorticoid and mineralocorticoid receptors, it has less potent toxicity than dexamethasone, suggesting that appropriate use of hydrocortisone may not develop complications such as brain toxicity. A current practice survey showed that hydrocortisone treatment has already been implemented in many neonatal units across the world.[24] Hydrocortisone use can also counter the untoward effects of cytokines and hemodynamic shock on cellular toxicity [25] and may improve the inflammatory process and effectively reduce cytokine- and hypofusion-induced cellular and white matter injury. Our study has several limitations in its observational nature: (i) the retrospective study design, which might not be appropriate for confirming the examined relationships; (ii) the relatively small sample size of the study group; (iii) hidden disabilities may subsequently have become apparent later, and many infants might have important developmental lags that were not classified as impairments; and (iv) many clinical conditions that may originate from prematurity itself. However, the strength of our study is the observation of neurodevelopmental outcomes by the Bayley Scales of Infant and Toddler Development III at a corrected age of 18 months as a long-term study.

In summary, we concluded that refractory hypotension within a week of life and seizures may be predictors of the severity of IVH. Severe IVH (grades 3–4) was also significantly associated with an

increased risk of neurodevelopmental outcome at corrected 18 months.

Abbreviations

VLBWI
very low birth weight infants
RDS
respiratory distress syndrome
IVH
intraventricular hemorrhage
NEC
necrotizing enterocolitis
BPD
bronchopulmonary dysplasia
ROP
retinopathy of prematurity
PVL
periventricular leukomalacia

Declarations

Conflict of Interest

YoungAh Youn wrote the first draft of the manuscript, and no honorarium, grant, or other form of payment was received to produce this manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and take full responsibility for the manuscript. We report no conflicts of interest.

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Tables

Table I. Clinical characteristics and outcomes of VLBWIs (n=191)

	No IVH (n = 55)	IVH (n = 136)	P-value
Gestational age, week	28.58 ± 2.75	27.54 ± 2.37	0.009[a]
Birth weight, kg	1.103 ± 0.302	1.042 ± 0.260	0.163
Male, n (%)	24 (43.6%)	76 (55.9%)	0.125
Maternal chorioamnionitis	14 (25.5)	51 (37.5)	0.112
Antenatal steroid use	36 (65.5)	82 (60.3)	0.506
Refractory hypotension ≤ 1 week of life	23 (41.8)	65 (47.8)	0.453
Resuscitation at the time of delivery#	50 (90.9)	128 (94.1)	0.425
RDS	47 (85.5)	129 (94.9)	0.029[a]
Surfactant > 2 times	15 (27.3)	56 (41.2)	0.072
Pneumothorax	5 (9.1)	20 (14.7)	0.297
Pulmonary hemorrhage	7 (12.7)	33 (24.3)	0.076
Pulmonary hypertension†	6 (10.9)	23 (16.9)	0.295
Neonatal seizure	13 (23.6)	86 (63.2)	< 0.001[a]
Sepsis	15 (27.3)	60 (44.1)	< 0.031[a]
PDA ligation	4 (7.3)	24 (17.6)	0.066
NEC operation	0 (0)	7 (5.1)	0.196
ROP operation	1 (1.8)	10 (7.4)	0.182
PRC transfusion	47 (85.5)	132 (97.1)	0.003[a]
BPD ≥ moderate	14 (25.5)	82 (60.3)	< 0.001[a]
PVL	5 (9.1)	67 (49.3)	< 0.001[a]
TPN duration‡	25.11 ± 25.11	43.36 ± 31.72	< 0.001[a]
Mechanical ventilation, days‡	12.85 ± 23.82	27.17 ± 31.62	0.001[a]

[a]P<0.05

[#]Resuscitation included oxygen use or positive pressure ventilation or intubation

[†]Use of nitric oxide, sildenafil within 1 week of birth

[‡]Expired patients were excluded

	No IVH (n = 55)	IVH (n = 136)	P-value
Hospital stay, days‡	35.11 ± 27.96	62.59 ± 38.41	< 0.001[a]
Mortality	16 (29.1)	26 (19.1)	0.132
[a]P<0.05			
[#]Resuscitation included oxygen use or positive pressure ventilation or intubation			
[†]Use of nitric oxide, sildenafil within 1 week of birth			
[‡]Expired patients were excluded			

Table II. Clinical characteristics and outcomes of VLBWIs with IVH (n=136)

	Mild IVH (Grades 1–2) (n = 81)	Severe IVH (grades 3–4) (n = 55)	P-value
Gestational age, week	27.94 ± 2.23	26.95 ± 2.47	0.016[a]
Birth weight, kg	1.07 ± 0.24	1.01 ± 0.29	0.224
Male, n (%)	40 (49.4)	36 (65.5)	0.064
Antenatal steroid use	42 (51.9)	40 (72.7)	0.015 [a]
Refractory hypotension ≤ 1 week of life	27 (33.3)	38 (69.1)	< 0.001[a]
Maternal chorioamnionitis	26 (32.1)	25 (45.5)	0.114
Resuscitation at delivery*	73 (90.1)	55 (100.0)	0.021[a]
RDS	76 (93.8)	53 (96.4)	0.701
Surfactant > 2 times	32 (39.5)	24 (43.6)	0.631
Pneumothorax	9 (11.1)	11 (20.0)	0.151
Pulmonary hemorrhage	13 (16.0)	20 (36.4)	0.007[a]
Pulmonary hypertension†	10 (12.3)	13 (23.6)	0.085
Neonatal seizure	40 (49.4)	46 (83.6)	< 0.001[a]
Sepsis	32 (39.5)	28 (50.9)	0.189
PDA ligation	17 (21.0)	7 (12.7)	0.215
NEC operation	5 (6.2)	2 (3.6)	0.701
ROP operation	4 (4.9)	6 (10.9)	0.190
BPD ≥ moderate	49 (60.5)	33 (60.0)	0.954
PVL	31 (38.3)	36 (65.5)	0.002
PRC transfusion	77 (95.1)	55 (100)	0.147
TPN duration‡	43.25 ± 27.0	43.53 ± 37.9	0.960

[a]P<0.05

[#]Resuscitation included oxygen use or positive pressure ventilation or intubation

[†]Use of nitric oxide, sildenafil or iloprost within 1 week of birth

[‡]Expired patients were excluded

	Mild IVH (Grades 1–2) (n = 81)	Severe IVH (grades 3–4) (n = 55)	P-value
Mechanical ventilation, days‡	23.84 ± 25.9	32.07 ± 38.25	0.137
Hospital stay, days‡	60.98 ± 27.54	64.96 ± 50.56	0.595
Mortality	7 (8.3)	19 (34.5)	< 0.001[a]
[a]P<0.05			
[#]Resuscitation included oxygen use or positive pressure ventilation or intubation			
[†]Use of nitric oxide, sildenafil or iloprost within 1 week of birth			
[‡]Expired patients were excluded			

Table III. Severe IVH (adjusted for gestational age, refractory hypotension, pulmonary hemorrhage and neonatal seizure) in a multiple logistic regression analysis (n=55)

	P	OR	95% CI
Gestational age, week	0.487	0.937	0.780–1.126
Refractory hypotension	0.025	2.746	1.133–6.652
Pulmonary hemorrhage	0.571	1.323	0.502–3.488
Neonatal seizure	0.042	2.689	1.038–6.968

Table IV. Neurodevelopmental outcomes of severe IVH on Bayley Scales of Infant and Toddler Development III at corrected18 months (n=136)

	Severe IVH (grade 3–4) (n = 55)	Mild IVH (Grades 1–2) (n = 81)	P-value
Score, mean ± SD			
Cognitive	74.89 ± 27.24	88.61 ± 23.01	0.023
Language	73.64 ± 22.38	85.43 ± 20.81	0.025
Motor	68.78 ± 26.10	81.52 ± 23.84	0.035
Socio-emotional score	79.26 ± 18.95	88.95 ± 20.64	0.049
Adaptive behavior score	73.68 ± 20.80	85.31 ± 16.12	0.043
At risk, n (%)[a]			
-Cognitive score	13 (37.1)	8 (13.6)	0.008 [a]
-Language score	13 (37.1)	10 (16.9)	0.028 [a]
-Motor score	15 (42.9)	13 (21.7)	0.029 [a]
-Socio-emotional score	10 (28.6)	5 (8.5)	0.010 [a]
-Adaptive behavior score	16 (45.7)	10 (16.9)	0.003 [a]

Table V. Outcomes of refractory hypotension ≤ 1 week on Bayley Scales of Infant and Toddler Development III at 18 months (n=92)

	Hypotension ≤ 1 week (n = 52)	No hypotension (n = 40)	P-value
Score, mean ± SD			
Cognitive	73.98 ± 21.77	89.50 ± 25.57	0.018
Language	76.69 ± 19.80	87.50 ± 23.09	0.022
Motor	78.62 ± 23.23	86.09 ± 25.03	0.036
At risk, n (%)[a]			
-Cognitive score	17 (32.7)	4 (10.0)	0.021
-Language score	17 (32.7)	4 (10.0)	0.021
-Motor score	23 (44.2)	7 (17.5)	0.028