Clinics in Surgery

Research Article
Published: 01 Oct, 2019

Early Hydrocortisone Use and Severe Retinopathy of Prematurity in Very Low Birth Weight Infants

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Abstract

Aim: To examine an association between early postnatal hydrocortisone (≤ 1 week of life) exposure and increased development of severe Retinopathy of Prematurity (ROP) in Very Low Birth Weight Infants (VLBWI).

Methods: Between Jan 2012 and Dec 2015, the clinical data of 279 VLBWI admitted were analyzed. Of a total 279 VLBWI, 28.0% (78/279) had ROP, and 16.8% had severe ROP; 20 (7.1%) neonates eventually underwent a laser operation for progressive ROP.

Results: VLBWI exposed to early postnatal hydrocortisone ≤ 1 week of life had higher hospital morbidities. Severe ROP occurred significantly more in the group exposed to early postnatal hydrocortisone. However, the multivariable logistic regression analysis showed that early postnatal hydrocortisone use was not consistently associated with severe ROP.

Conclusion: The use of early postnatal hydrocortisone may be a marker for the severity of illness due to prematurity.

Keywords: Steroid; Retinopathy of prematurity; Outcomes; Risk factor

Abbreviations

VLBWI: Very Low Birth Weight Infants; ROP: Retinopathy of Prematurity; RDS: Respiratory Distress Syndrome; BPD: Broncho Pulmonary Dysplasia; NEC: Necrotizing Enterocolitis; IVH: Intraventricular Hemorrhage

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 (VLBWI). The increased survival rate in this population has resulted in a higher risk for developing complications such as Retinopathy of Prematurity (ROP). ROP pathogenesis is multifactorial and is known to be associated with a low gestational age and birth weight and the uncontrolled use of oxygen therapy. Along with additional postnatal risk factors for the development of ROP, such as frequent apnea, sepsis, a history of surfactant treatment, multiple transfusions, anemia, or multiple births, postnatal steroid use is additionally reported to increase the development of ROP [1-5]. Corticosteroids are frequently administered to VLBWI to treat established or evolving chronic lung disease [1]. In two separate recent Cochrane reviews, meta-analyses were performed to examine the effect of the timing of steroid administration on the risk of various outcomes (including ROP) for preterm infants [1,2]. These reviews reported that the late use of steroids (initiated after 1 week of life) significantly increased the risk of ROP, whereas the early use of steroids (initiated within one week of life) significantly decreased the risk [1,6]. Many Randomized and Control Trials (RCTs) have shown adverse neuro developmental outcomes after postnatal dexamethasone treatment for BPD; no multicenter RCT studies have demonstrated adverse effects on the long-term outcomes after hydrocortisone therapy [3]. Since 2014, we used hydrocortisone (no dexamethasone) within a week of life in our clinical practice only to manage clinical conditions, such as adrenal insufficiency, shock and Respiratory Distress Syndrome (RDS), and we used it as an alternative to dexamethasone in an attempt to minimize adverse long-term neurological outcomes. In our study, we assessed the association between postnatal hydrocortisone use ≤ 1 week of life and the development of severe ROP and those who required laser treatment. The goal of this study was to assess the association of early hydrocortisone use to the development of severe ROP in VLBWI.

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Received Date: *12 Aug 2019*
Accepted Date: *26 Sep 2019*
Published Date: *01 Oct 2019*

Citation:
Kim B-J, Seo Y-M, Yum S-K, Sung I-K, Youn YA. Early Hydrocortisone Use and Severe Retinopathy of Prematurity in Very Low Birth Weight Infants. Clin Surg. 2019; 4: 2599.

Materials and Methods

We analyzed the demographic and clinical data obtained from reviewing the medical records of 279 VLBWI who were examined for ROP during this period at Seoul St. Mary's Hospital between Jan 2012 and Dec 2015. We followed the methods of Young Ah Youn et al. [7]. The VLBWI were subdivided into early postnatal hydrocortisone and no early hydrocortisone groups. VLBWI who were exposed to hydrocortisone (5 mg/kg/day IV, divided into 3 doses at 8-hour intervals) ≤ 1 week of life for clinical reasons, such as hypotension, shock and RDS in our NICU, were grouped as the early hydrocortisone exposure group. The clinical factors influencing the development of severe ROP were analyzed. The study was approved by the Ethics Committee of Seoul St. Mary's Hospital.

Identification of treated infants

Our study included VLBWI screened for ROP with birth weight <1500 g and gestational age <32 weeks at birth. Those who survived until the initial ophthalmologic examination was performed between the 4th and 6th week after birth were examined until resolution or effective stabilization of retinopathy was achieved after treatment.

Definitions

ROP was defined according to the International Classification of Diseases for ROP. Severe ROP was defined in patients exhibiting greater than stage 2 (International Classification of ROP) or in those who required laser treatment in this study [8]. Early steroid exposure included hydrocortisone use for any indication within a week of life.

Massive pulmonary hemorrhage was defined as pulmonary hemorrhage, which affects vital signs as manifested by cardiovascular collapse or acute respiratory failure. Pulmonary hypertension is defined by the need to use nitric oxide or sildenafil or iloprost ≤ 1 week of life. Broncho Pulmonary Dysplasia (BPD) was diagnosed if oxygen use exceeding 0.21% was still needed at a corrected gestational age of 36 weeks. Necrotizing Enterocolitis (NEC) was defined as grade II or higher using Bell's classification. Intraventricular Hemorrhage (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.

Statistical analysis

Continuous variables were compared using Student's t-test and are expressed as the mean ± standard deviation values. Discrete variables were compared using a χ^2 test or Fisher's exact test and are expressed as percentages. All of the analyses were two-tailed, and clinical significance was defined as a p value lower than 0.05. To seek any confounding risk factors for severe ROP, 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 ROP and a stepwise logistic regression analysis: gestational age, birth weight, pulmonary hemorrhage, and pulmonary hypertension. All of the 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 279 neonates with ≤ 1500 g birth weight who were admitted to the neonatal intensive care unit between January 2012 to December 2015, 28.0% (78/279) of VLBWI had ROP and 16.8% (47/279) had severe ROP. Further, 20 (7.1%) VLBWI eventually underwent a laser operation for progressive ROP. Table 1 compares the clinical characteristics; VLBWI with ROP had a significantly lower gestational age (27.7 ± 13.7 weeks vs. 28.8 ± 21.5 weeks, p<0.001) and birth weight (1027.4 ± 218.3 g *vs.* 1105.3 ± 287 g, p=0.002). Early postnatal hydrocortisone use was used significantly more frequently in the ROP group (p=0.017) with regard to morbidities, infants who developed ROP had significantly more neonatal seizure, sepsis, Patent Ductus Arteriosus (PDA) ligation, Necrotizing Enterocolitis (NEC) operation, laser treatment for ROP, BPD ≥ moderate and PVL. Additionally, they had more packed red cell (PRC) transfusions as well as a longer Total Parenteral Nutrition (TPN), mechanical ventilation duration and hospital stay (p<0.001). The hospital mortality rate was significantly higher in the ROP group.

Table 1: Clinical characteristics of VLBWIs (n=279).

	No ROP (n=201)	**ROP** (n=78)	*P*
Gestational age, week	28.8 ± 21.5	27.7 ± 13.7	<0.001[a]
Birth weight, g	1105.3 ± 287	1027.4 ± 218.3	0.002[a]
Male, n (%)	7.26 ± 0.2	7.27 ± 0.1	0.125
Initial pH ≤ 1 hr of life	120 (93.0)	62 (100)	0.095
Maternal chorioamnionitis	63 (31.3)	26 (33.3)	0.749
Antenatal steroid use	112 (56.0)	45 (57.7)	0.798
Early hydrocortisone use	105 (52.2)	53 (67.9)	0.017[a]
Resuscitation at the time of delivery#	181 (91.0)	71 (97.3)	0.077
RDS	168 (84.0)	74 (94.9)	0.015[a]
Surfactant >2 times	59 (29.3)	21 (26.9)	0.010[a]
Pneumothorax	22 (10.9)	5 (6.4)	0.250
Massive pulmonary hemorrhage	41 (20.4)	18 (23.1)	0.623
Pulmonary hypertension†	29 (14.4)	10 (12.8)	0.728
Neonatal seizure	68 (33.8)	46 (59.0)	<0.001[a]
IVH > grade II	42 (22.5)	25 (32.1)	0.107
Sepsis	70 (34.8)	45 (57.7)	<0.001[a]
PDA ligation	24 (11.9)	22(28.2)	0.001[a]
NEC operation	3 (27.3)	5 (35.7)	0.635
ROP operation	0 (0)	20 (25.6)	<0.001[a]
PRC transfusion	175 (87.1)	77 (98.7)	0.003[a]
BPD ≥ moderate	85 (42.3)	69 (88.5)	<0.001[a]
PVL	39 (21.0)	34 (44.2)	<0.001[a]
TPN duration‡	23.5 ± 22.1	55.8 ± 33.9	<0.001[a]
Mechanical ventilation, days‡	21.2 ± 21.3	52.2 ± 40.8	<0.001[a]
Hospital stay, days‡	29.8 ± 2.6	37.6 ± 4.7	<0.001[a]
Mortality	3 (1.5)	5 (6.4)	0.0470[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

Abbreviations: VLBWI: Very Low Birth Weight Infants; ROP: Retinopathy of Prematurity; g: Gram Body Weight; RDS: Respiratory Distress Syndrome; IVH: Intraventricular Hemorrhage; PDA: Patent Ductus Arteriosus; NEC: Necrotizing Enterocolitis; PRC: Packed Red Cells; BPD: Bronchopulmonary Dysplasia; PVL: Periventricular Leukomalacia; TPN: Total Parenteral Nutrition

Table 2 provides the degree of severity among the infants diagnosed with ROP. Among the VLBWI with ROP (n=78), the severe ROP group exhibited a significantly lower gestational age (27.0 ± 14.0 weeks *vs.* 28.0 ± 13.0 weeks, p=0.046) and birth weight (959.6 ±

Table 2: Clinical characteristics of VLBWIs with ROP (n=78).

	ROP (n=31)	**Severe ROP** (n=47)	*P*
Gestational age, week	28.0 ± 13.0	27.0 ± 14.0	0.046[a]
Birth weight, g	1099.7 ± 203.7	959.6 ± 216.4	<0.00[a]
Male, n (%)	9 (34.6)	19 (52.8)	0.200
Antenatal steroid use	18 (58.1)	27 (57.4)	0.957
Postnatal steroid use	19 (61.3)	33 (70.2)	0.413
Maternal chorioamnionitis	8 (25.8)	18 (38.3)	0.252
Resuscitation at delivery*	29 (96.7)	42 (97.7)	0.795
RDS	117 (91.4)	59 (95.2)	0.354
Surfactant >2 times	45 (34.8)	26 (40.0)	0.010[a]
Pneumothorax	1 (3.2)	4 (8.5)	0.351
Massive pulmonary hemorrhage	3 (9.7)	15 (31.9)	0.023[a]
Pulmonary hypertension†	3 (9.7)	7 (14.9)	0.500
Neonatal seizure	18 (58.1)	28 (59.6)	0.894
IVH > grade II	8 (25.8)	17 (36.2)	0.337
Sepsis	15 (48.4)	30 (63.8)	0.177
PDA ligation	11 (35.5)	11 (23.4)	0.246
NEC operation	1 (25.0)	4 (40.0)	0.597
ROP operation	2 (6.5)	18 (38.3)	0.002[a]
BPD ≥ moderate	25 (80.6)	44 (9306)	0.079[a]
PVL	11 (36.7)	23 (48.9)	0.294
PRC transfusion	30 (96.8)	47 (100)	0.215
TPN duration‡	40.8 ± 19.3	65.7 ± 37.8	0.028[a]
Mechanical ventilation, days‡	21.2 ± 21.3	52.2 ± 40.8	0.036[a]
Hospital stay, days‡	64.7 ± 20.3	93.1 ± 39.1	0.015[a]
Mortality	0 (0)	8 (10.3)	<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
Abbreviations: VLBWI: Very Low Birth Weight Infants; ROP: Retinopathy of Prematurity; g: Gram Body Weight; RDS: Respiratory Distress Syndrome; IVH: Intraventricular Hemorrhage; PDA: Patent Ductus Arteriosus; NEC: Necrotizing Enterocolitis; PRC: Packed Red Cells; BPD: Bronchopulmonary Dysplasia; PVL: Periventricular Leukomalacia; TPN: Total Parenteral Nutrition

Table 3: Risks for ROP (adjusted for gestational age, birth weight, resuscitation at delivery, pulmonary hemorrhage, IVH > grade II and PVL) in a multiple logistic regression analysis.

	P	OR	95% CI
Gestational age, week	0.074	0.853	0.716-1.016
Birth weight, gram	0.944	1.000	0.998-1.002
Resuscitation at delivery	0.340	2.123	0.452-9.968
Pulmonary hemorrhage	0.221	0.616	0.284-1.338
IVH > grade II	0.755	0.894	0.441-1.812
PVL	0.006	2.552	1.300-5.009
Early hydrocortisone use	0.171	1.613	0.813-3.198

Abbreviations: IVH: Intraventricular Hemorrhage; PVL: Periventricular Leukomalacia

216.4 g *vs.* 1099.7 ± 203.7 g, p<0.001). Surfactant >2 times and massive pulmonary hypertension were significantly more frequent in the severe ROP group (p<0.05). For morbidities, the severe ROP group underwent significantly more laser operations and had a longer TPN, mechanical ventilation duration and hospital stay (p<0.05). The ROP

Table 4: Risks for severe ROP (adjusted for gestational age, birth weight, resuscitation at delivery, pulmonary hemorrhage, IVH > grade II and PVL) in a multiple logistic regression analysis.

	P	OR	95% CI
Gestational age, week	0.557	1.237	0.608-2.516
Birth weight, gram	0.848	1.000	0.997-1.004
Resuscitation at delivery	0.481	2.120	0.262-17.153
Pulmonary hemorrhage	0.340	1.476	0.664-3.281
IVH > grade II	0.646	1.208	0.540-2.699
PVL	0.067	2.051	0.950-4.428
Early hydrocortisone use	0.114	1.964	0.850-4.540

Abbreviations: IVH: Intraventricular Hemorrhage; PVL: Periventricular Leukomalacia

laser operation was performed in 18 infants in the severe ROP group. Mortality occurred only in the VLBWI in the severe ROP group. To explore the influence of any possible confounding factors on severe ROP in VLBWI, we performed a multivariable logistic regression analysis to identify any confounding factors related to severe ROP. Table 3 provides the risks for ROP and Table 4 the risks for severe ROP in a logistic regression analysis. We included gestational age, birth weight, resuscitation at the time of delivery, massive pulmonary hemorrhage, IVH > grade II, and PVL along with early postnatal steroid use in this analysis. Early postnatal hydrocortisone use was not consistently associated with either ROP or severe ROP.

Discussion

In our study of VLBWI, we observed 279 Korean VLBWI who were admitted to our NICU during the study period. We found that early postnatal hydrocortisone exposure within the first week of life was not associated with severe ROP, but the use of early postnatal hydrocortisone may be a marker for severity of illness due to prematurity and appropriate use of steroid may not contribute to the development of severe ROP. Rather, the Cochrane database analysis [9] revealed that the early administration of systemic steroids (up to 96 h of age) to prevent BPD led to a reduction in severe ROP. On contrary, Karna et al. [10] showed that late (beyond 3 weeks) and prolonged (>2 weeks) administration of postnatal steroids was significantly associated with a four-fold increase of risk for ROP. The role of steroids in the pathogenesis of ROP is still controversial. Uemura et al. [11] reported that steroid-induced vaso-proliferative retinopathy occurred in young rabbits following dexamethasone treatment in an animal study. Younger animals were more likely to develop retinopathy than older ones were. The steroid induced retinopathy differed from oxygen-induced retinopathy in that it occurred without a vaso-obliterative phase; the morphology of the vaso-proliferation was different in steroid-induced retinopathy compared with oxygen-induced retinopathy. In our study, early steroid use was defined as early as the use within a week of life, and our center only used hydrocortisone as an alternative to dexamethasone to minimize negative effect on neurodevelopmental outcomes.

The worse hospital morbidities in the VLBWI exposed to early hydrocortisone in our study may not be directly related to steroid use, but the steroid-treated infants were more severely ill than were the VLBWI without steroid exposure. A meta-analyses of prospective, randomized, placebo-controlled trials found no effect on the incidence of severe ROP when postnatal steroids were used early (within 96 h after birth, eight studies, 1,453 infants) or within 7 to 14 days of life (five studies, 247 infants) for treatment of CLD

[10,12]. These trials summarized that late steroid use (>1 week of life) significantly increased ROP risk whereas early steroid use (≤ 1 week of life) significantly decreased risks. Our steroid was used early which may benefit for severe illness due to prematurity among VLBWI. Interventions for treating adrenal insufficiency, shock or RDS were additionally implicated in the pathogenesis of ROP. In a study, a critically low birth weight infants (<500 g) who was more commonly exposed to postnatal steroids was reported to develop more ROP [13].

As risk factors, small for gestational age among premature infants can also be a risk factor for ROP [14]. Kim et al. [5] demonstrated that surfactant was a significant independent risk factor for ROP. Initial birth weight <1250 g with formula consumption instead of breast milk are recently reported risk factors o for the development of ROP [15]. Furthermore, insulin like growth factor (IGF)-1 [16], apnea [5], hypoxia [17], bacterial and fungal late-onset sepsis [18] have been previously reported to increase ROP risk. BPD, durations of oxygen therapy, mechanical ventilation and length of hospitalization were shown to be significant risk factors for ROP [19]. Our study supports the numerous previous studies that reported on ROP risk factors. In addition to lower gestational age and lower birth weight, our Korean VLBWI with ROP had a longer TPN, mechanical ventilation duration, hospital stay and higher mortality rate [20]. A longer hospitalization duration was also shown to be a risk factor for ROP and indicated a more complicated respiratory course in VLBWI who require more interventions, such as surfactant, high-frequency ventilator care and oxygen therapy, and who often develop BPD and ROP [21].

Our study has several limitations: (i) the retrospective study design, which might not be appropriate for confirming the examined relationships; (ii) the relatively small sample size of the study groups; and (iii) many clinical conditions that comingle, originating from prematurity itself.

In summary, we concluded that early postnatal hydrocortisone use (5 mg/kg/day for unstable clinical reasons, such as hypotension and shock) at ≤ 1 week of life may not increase the risk for severe ROP. The use of early postnatal hydrocortisone may also be a marker for the severity of illness. Appropriate use of steroid for unstable clinical settings in VLBWI may be useful, however, due to concerns of the adverse effect on the neurodevelopment outcomes, lowering the hydrocortisone dosage may also be considered in the future. Since children with a history of ROP can later develop other ocular disorders in life [22], ROP risks should further studied and evaluated in the future.

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