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Dopamine-resistant hypotension and severe retinopathy of prematurity

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Abstract

Objective—To examine the relationship between the cause or severity of hypotension and the development of severe retinopathy of prematurity (sROP) (≥ stage 3 or stage 2 with plus disease in Zone I or II)..

Study design—Infants (<28 weeks' gestation, n=242) were observed for hypotension and treated with a standardized hypotension-treatment protocol. Hypotension was classified as resulting from one of the following causes: (a) culture-positive infection and/or necrotizing enterocolitis, (b) PDA ligation, or (c) "idiopathic" (no cause identified other than prematurity), and as being either dopamine-responsive or dopamine-resistant. Cortisol levels were measured for infants with dopamine-resistant hypotension. Eye examinations were performed until the ROP resolved or the vasculature matured. Multivariable logistic regression analysis was performed to determine the relationship between the cause/severity of hypotension and sROP.

Results—Overall, 66% of infants developed hypotension (41% were dopamine-responsive and 25% were dopamine-resistant). sROP developed in 19% of infants. "Idiopathic" dopamine-resistant hypotension was the only cause significantly related to sROP. 66% of infants with dopamine-resistant hypotension had low serum cortisol (≤10 μg/dL). Low cortisol, in the presence of dopamine-resistant hypotension, was significantly associated with sROP and accounted for the relationship between "idiopathic" hypotension and sROP. When low cortisol was included in statistical models, other known risk factors, such as immature gestation, were no longer significantly related to sROP.

Conclusion—Low cortisol, in the presence of dopamine-resistant hypotension, has the greatest magnitude of association with sROP.

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Keywords

retinopathy of prematurity; ROP; hydrocortisone; dopamine; newborn hypotension; cortisol; adrenal insufficiency

Approximately 16% of extremely premature infants develop a severe form of retinopathy of prematurity (ROP) and 12% meet criteria for treatment (1). Although several risk factors (such as preeclampsia, respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD), necrotizing entercolitis (NEC), patent ductus arterious (PDA), and duration of respiratory support (2, 3)) have been associated with the development of severe ROP, immature gestational age is the most consistent predictor (4).

Elevated circulating cytokines are associated with ROP in preterm infants (5). Inflammatory cytokines have the ability to modulate blood pressure as well as angiogenesis. Although hypotension has been identified as a predictor of severe ROP (2, 6), this relationship has not been consistently observed (3, 7). Unfortunately, none of the studies that have considered the association between hypotension and ROP has examined whether the relationship depends on the cause or severity of the hypotension. Hypotension is frequently associated with inflammatory states such as infection, NEC or following neonatal surgeries (like PDA ligation) (8, 9). However, most episodes of neonatal hypotension are not attributable to any identifiable causes and are thought to result from immature cardiovascular regulation ("idiopathic") (8).

Neonatal hypotension and altered regulation of vascular tone are primarily determined by postmenstrual age (10). In most circumstances, low blood pressure can be normalized by catecholamine (dopamine) infusions; in some instances, low blood pressure fails to respond to dopamine alone and other treatments are needed to bring the blood pressure into the range of normally distributed (age-appropriate) blood pressures.

Cortisol is crucial to controlling inflammation. In its absence, inflammatory responses are amplified (11). Recent studies demonstrate that premature infants frequently have low serum cortisol concentrations during states of physiologic stress (12)(13, 14), and that premature birth produces an inflammatory state even in the absence of identifiable inflammatory processes (15).

We hypothesized that severe degrees of neonatal hypotension might be associated with the development of ROP and that the severity of the hypotension might be predictive of the degree of ROP. We speculated that if an association between altered vascular tone/ hypotension and abnormal retinal vascular development did exist, an imbalance between inflammatory mediator production and cortisol production might be responsible for the association.

METHODS

This project was approved by the University of California San Francisco's Institutional Review Board. A single neonatologist (RIC) prospectively evaluated and recorded the perinatal and in-hospital neonatal risk factors (known to be associated with ROP) from all infants ≤ 27–6/7 weeks' gestation admitted within the first 24 hours of birth to the William H. Tooley Intensive Care Nursery at the University of California San Francisco between January 2004 and December 2011. Three hundred patients were eligible for the study; fifty-eight died prior to 35 weeks' corrected age (before their retinal vasculature matured). Perinatal and neonatal characteristics of the remaining 242 infants are listed in Table I. Criteria used to evaluate specific neonatal risk factors were previously described (16, 17).

All infants received a course of indomethacin within the first days after birth (for PDA prevention); the indomethacin treatment approach and follow up PDA management have been previously described (16). Oxygen Saturation target limits for infants in the study population were 88–94%. Two pediatric ophthalmologists (WVG, AdAC) performed all eye examinations. The criteria for diagnosis of ROP and examination schedule were previously described (17). Follow up examinations were performed until there was resolution of the ROP and/or the retinal vasculature matured. The international classification of ROP was used to classify the severity of ROP (17). Our primary outcome was "severe ROP", which we defined as ≥ stage 3 ROP, or stage 2 ROP with plus disease in Zone I or II.

Blood pressure was measured directly with a transducer connected to an indwelling arterial catheter, or noninvasively using the oscillometric method. An arterial line and transducer were used to measure blood pressure continuously in all infants receiving catecholamine infusions or hydrocortisone for blood pressure support. Our nursery has specific guidelines defining what constitutes low blood pressure and when to treat. Hypotension is defined as: mean BP less than the 3rd percentile for postmenstrual age (10). Operationally this means that infants are considered to be hypotensive, and require treatment for their hypotension, if their mean blood pressure is less than [(postmenstrual age in mm Hg) - (3 to 4 mm Hg)]. For infants who fail to maintain an *adequate mean blood pressure* (i.e., mean blood pressure greater than the hypotensive range) for greater than 15 minutes, two fluid boluses (isotonic saline 10 mL/kg per bolus) can be given initially. If the fluid boluses are unsuccessful in maintaining an *adequate mean blood pressure,* a dopamine infusion is added. Dopamine infusions are started at a rate of 5 μg/kg/min, and increased by 2.5 μg/kg/min every 15–30 minutes until an *adequate mean blood pressure* (above the hypotensive range) is achieved. If 18–20 μg/kg/min dopamine fails to maintain an *adequate mean blood pressure*, hydrocortisone (1 mg/kg/day IV, divided into 4 doses at 6-hour intervals) is added. Hydrocortisone is not used at lower infusion rates of dopamine. If this fails to maintain an *adequate mean blood pressure*, the dose of hydrocortisone can be increased to 3 mg/kg/day. Once an *adequate mean blood pressure* has been maintained for >2 hours, weaning of a vasopressor can be initiated at the same rate it was increased.

Patients were considered to have treated *hypotension* if they received dopamine; to have *dopamine-responsive hypotension* if an adequate blood pressure could be maintained with infusions of dopamine (<18–20 μg/kg/min) alone; to have severe *dopamine-resistant hypotension* if they received hydrocortisone for their hypotension. Information about the cause of the hypotension, medications used to treat the hypotension, and the duration of treatment were from the medical records and verified with an electronic pharmacy database which recorded medications, dosage and days of treatment. Infants who developed "severe" dopamine-resistant hypotension were classified as having received hydrocortisone for hypotension due to one of the following causes: (a) sepsis (i.e., associated with any culture-positive infection and/or necrotizing enterocolitis), (b) PDA ligation, or (c) "idiopathic" (no cause other than prematurity identified). Serum collected prior to the first dose of hydrocortisone was used to determine cortisol concentrations in infants with dopamine-resistant hypotension. Cortisol was measured by competitive chemiluminescent immunoassay using the Siemens ADVIA Centaur System. The results of the cortisol measurements were not available prior to starting the hydrocortisone.

Statistical Analyses

The χ^2 test was used to compare categorical risk factors and outcomes, and the Student's t-test was used to compare mean values of continuous variables. The ANOVA test was used to analyze the relationships between the means of several groups. An adjusted multivariable logistic regression model was used to determine the effects of specific hypotension-related predictive variables on the outcome of interest (severe ROP). We first identified the non-

hypotension-related perinatal and neonatal risk factors that were most associated with severe ROP using bivariate analyses. A model was built for the outcome of interest through forward selection. Variables were added to the model in order of increasing statistical significance. Variables were dropped from the model if their p-value rose to ≥ 0.2 after the addition of other variables.

After the model was built, each of the hypotension-related predictive variables was individually forced into the model to evaluate its effect when adjusted by the other predictors. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using the multivariable model. A p-value of <0.05 for the predictive variables was considered significant.

Area under the Receiver Operating Characteristic was used to determine how well dopamine-resistant hypotension discriminated between those with and without severe ROP. All analyses were performed using STATA 11 (College Station, TX) statistical software.

RESULTS

Hypotension was a frequent occurrence among our 242 study infants: 41% developed dopamine-responsive hypotension; 25% developed dopamine-resistant hypotension (either due to infection/NEC [3%], ligation [5%], or “idiopathic” [17%]). Forty-five infants were diagnosed with severe ROP; 39 received laser treatment; 6 infants with stage 3 disease alone did not meet criteria for treatment (Table I) (17). As has been observed in prior studies, infants that developed severe ROP were more likely to be immature, be small for gestational age, receive increased fluid volumes during the first 96 hours after birth, and develop bronchopulmonary dysplasia (Table I). In the bivariate analysis, hypotension (treated with hydrocortisone and/or dopamine) was associated with severe ROP.

We used a multivariable model that included all of the potential non-hemodynamic risk factors for severe ROP (Table II), to determine if the hemodynamic risk factors were independently associated with severe ROP.

In the multivariable model, infants that were treated with dopamine, by itself, were not at significant risk for developing severe ROP (Table III). Only infants with hydrocortisone-treated, dopamine-resistant hypotension were at significant risk. The median duration of hydrocortisone treatment (≥ 1 mg/kg/d), for infants with dopamine-resistant hypotension, was 4 days (range: 0–30 days), and the median postnatal age when hydrocortisone treatment began was 14 days (range: 0–52 days). Both early and late presentations of dopamine-resistant hypotension and short and long durations of hydrocortisone treatment were associated with an increased risk for developing severe ROP.

Among the three potential causes of dopamine-resistant hypotension that we examined (“idiopathic”, infection or NEC, and following PDA ligation), “idiopathic” hypotension was the only cause significantly associated with severe ROP (Table III). Sixty-five percent of infants with “idiopathic” dopamine-resistant hypotension developed severe ROP (predictive sensitivity = 58%, specificity = 93%, area under the receiver operator curve = 0.75).

Patients are generally considered to have an inappropriate adrenal response to stress when their serum cortisol values are <15 μg/dL (18). Two-thirds of the infants with dopamine-resistant hypotension had low serum cortisol concentrations (≤10 μg/dL). The occurrence of low serum cortisol concentrations, in the presence of dopamine-resistant hypotension, was a significant risk factor for severe ROP (Table III; sensitivity = 61%, specificity = 94%, area under the receiver operator curve = 0.77).

Infants with "idiopathic" dopamine-resistant hypotension had lower cortisol concentrations (7±4 μg/dL) than infants with infection/NEC-related (34±31 μg/dL) or PDA ligation-related hypotension (21±48 μg/dL) (p=0.02). The low cortisol concentrations in the "idiopathic" hypotension group could account for the significant association between "idiopathic" hypotension and severe ROP. When low serum cortisol concentrations (≤10 μg/dL) were included as a variable in the statistical model, the etiologic subgroup, "idiopathic" hypotension, was no longer found to be independently associated with severe ROP (OR (without the variable *cortisol ≤10 μg/dL* in the model: 10.1, p< 0.001; OR (with the variable *cortisol ≤10 μg/dL* in the model: 1.5, p=NS).

To see if hydrocortisone treatment itself played a role in the development of severe ROP, we examined the relationship between hydrocortisone and severe ROP, when hydrocortisone was given for causes unrelated to hypotension. Ten normotensive infants were treated with hydrocortisone strictly for pulmonary reasons (either to facilitate extubation or for worsening chronic lung disease). The median duration and postnatal age at treatment was 3 days (range: 0–9 days) and 25 days (range: 9–53 days), respectively. There was no significant relationship between the use of hydrocortisone for pulmonary reasons and the development of severe ROP (OR=0.2, 95% CI=0.02–2.6, p=0.22).

DISCUSSION

Both the non-hemodynamic risk factors associated with severe ROP, and the incidence of severe ROP, were similar to previous reports (1–4). We found that dopamine-resistant hypotension was a significant and strong risk factor for the development of severe ROP in a model that controlled for other known risk factors (Table III). We used an operational definition of dopamine-resistant hypotension that was based on an infant having received hydrocortisone for this condition. The timing and treatment of hypotension was guided by a standardized protocol linked to the normal distribution of newborn blood pressures. Although blood pressure criteria are frequently used to determine treatment protocols (19, 20), they do not necessarily reflect the adequacy or inadequacy of specific organ perfusion, oxygenation, or tissue homeostasis (8, 20). Hydrocortisone was not used for blood pressure control unless dopamine failed to maintain an *adequate mean blood pressure* (see Methods for definition) at infusion rates greater than 18–20 μg/kg/min.

It is unlikely that the relationship between dopamine-resistant hypotension and severe ROP is due to the hydrocortisone. Although the association between postnatal steroids and ROP is controversial, most of the controversy arises from studies that focus on dexamethasone use for chronic lung disease. These controlled studies have observed: a) either a protective effect, b) no effect, or c) a negative effect of dexamethasone on ROP (21–23). Controlled studies that have looked specifically at hydrocortisone use in BPD found no effect on the risk of ROP (24, 25). Similarly, when hydrocortisone was evaluated in controlled trials to prevent BPD or to treat hypotension, no increased risk of ROP was observed (26). In addition, no increased risk of ROP was found in our study when normotensive infants were treated with hydrocortisone for pulmonary reasons.

We speculated that an imbalance between inflammatory mediator production and cortisol production might be responsible for the association between altered vascular tone/ hypotension and abnormal retinal vascular development. All three of the causes of dopamine-resistant hypotension ("idiopathic", infection or necrotizing enterocolitis, and following PDA ligation (27)) examined in our study are associated with increased inflammatory mediator production; however, only "idiopathic" hypotension was significantly associated with severe ROP (Table III). Conversely, two-thirds of the infants with dopamine-resistant hypotension had low serum cortisol concentrations (≤10 μg/dL),

and, in the presence of dopamine-resistant hypotension, low serum cortisol concentrations were significantly associated with severe ROP (Table III). When the variable "low serum cortisol concentrations" was included in the statistical model, we found that low serum cortisol concentrations (≤10 μg/dL) could account for the significant relationship between "idiopathic" hypotension and severe ROP.

Cortisol plays a crucial role in controlling inflammation. Sick, preterm infants have a bimodal distribution of cortisol concentrations: 30% have elevated concentrations, as expected for a stressed state; 70% have low concentrations (12). The low cortisol concentrations during stress do not appear to be due to low corticosteroid binding globulin or to diminished hypothalamic or pituitary responses to stress. Rather, they appear to be due to an immature adrenal response to elevated ACTH levels (13, 14). Although adrenal function usually returns to normal by the end of the second week of life (28), recent reports suggest that the impaired production of cortisol may persist for several weeks (13, 14).

Prior studies have noted an association between low basal (and ACTH-stimulated) cortisol levels and neonatal morbidities (hypotension and BPD) (13, 18, 28–31). However, this has not been observed consistently (29, 32–36). In addition, none of these studies found an association between depressed basal (or stimulated) cortisol concentrations and severe ROP (29, 32–36). Our study demonstrates that a specific subgroup of preterm infants, those who have low cortisol concentrations at the same time they are experiencing dopamine-resistant hypotension, have the greatest risk for developing severe ROP. When "low cortisol concentrations (≤10 μg/dL)" are included as a variable in our statistical models, other known risk factors for ROP, like gestational age, lose their significance ($OR_{gestational\ age}$ (without the variable *cortisol ≤10 μg/dL* in the model)=0.59 (CI: 0.42–0.84), p<0.003 (Table II) versus $OR_{gestational\ age}$ (with the variable *cortisol ≤10 μg/dL* in the model)=0.85 (CI: 0.54–1.32), p=0.46).

Although low cortisol concentrations in the presence of dopamine-resistant hypotension may reflect an inadequate stress reaction, we hypothesize that the depressed cortisol levels are not the cause of the subsequent severe ROP. Several randomized controlled trials have evaluated replacement hydrocortisone as either a preventative or treatment therapy; although ROP was not the primary outcome in any of the trials, none of them observed an effect on the incidence of severe ROP during the study (24–26, 30, 31). We speculate that a low cortisol concentration, in the presence of dopamine-resistant hypotension, reflects the persistence of an immature fetal state designed to protect the infant against high concentrations of catabolic hormones (37). As such, it serves as an important biomarker, identifying an extremely immature population of premature infants that may be highly vulnerable to the development of ROP. Future studies will be needed to test this hypothesis.

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Abbreviations

ROP	Retinopathy of prematurity
sROP	severe Retinopathy of prematurity
PDA	Patent ductus arteriosus
BPD	Bronchopulmonary dysplasia

NEC	Necrotizing enterocolitis
RSS	Respiratory severity score

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Table 1

Patient demographics and morbidities associated with retinopathy of prematurity - Bivariate analysis

	Retinopathy staging	
	None or mild ROP† N = 197	**Severe ROP† N = 45**
Non-Hemodynamic Risk Factors:		
Gestational age - weeks, mean (SD)†	26.2 ± 1.0	25.4 ± 1.1*
Gestational age <26 weeks - %	31	67*
Birthweight - grams, mean (SD)	867 ± 187	712 ± 151*
Small for Gestational Age - %	5	16*
Caucasian - %	40	42
Male sex - %	50	58
Antenatal Betamethasone - %†	79	78
Preeclampsia - %	20	22
Gestational Diabetes - %	8	7
Chorioamnionitis - %	23	27
Respiratory Distress Syndrome - %	91	93
Surfactant - %	92	100
RSS at 24 hours - units, mean (SD)†	1.8 ± 1.3	2.2 ± 0.8
Bronchopulmonary Dysplasia - %†	26	56*
Necrotizing Enterocolitis - %†	10	18
Intracranial Hemorrhage (Grades 3 or 4) - %	12	9
Cystic Periventricular Leukomalacia - %	12	11
Infection - %†	44	64*
Average daily fluids, mean (SD)†	147 ± 26	165 ± 32*
PDA after indomethacin treatment - %†	28	44*
Hemodynamic Risk Factors:		
Dopamine†	59	82*
Hydrocortisone-treated hypotension - any cause - %	15	69*
Hydrocortisone-treated hypotension - “idiopathic” - %	7	58*
Hydrocortisone-treated hypotension - “infection/NEC” - %	3	2
Hydrocortisone-treated hypotension - “post surgical/PDA ligation” - %†	5	9*
Hydrocortisone-treated hypotension - with serum cortisol ≤10 μg/dL - %†	6	60*

*p<0.05,

† Definitions: *Severe (ROP),* Retinopathy of prematurity: Stage 2 with plus disease or ≥ Stage 3; *Mild ROP*: ≤ Stage 2 without plus disease; *Gestation*, based on early (<24 weeks gestation) ultrasound dating; *Antenatal Betamethasone*, receipt of betamethasone more than 6 hours prior to delivery; *Respiratory Severity Score (RSS),* mean airway pressure x fraction of inspired oxygen, measured at 24 hours after birth; *Bronchopulmonary Dysplasia (BPD*), the need for supplemental oxygen to maintain oxygen saturation >90% at 36 weeks corrected age;

Necrotizing enterocolitis, Bell's classification ≥II (treated medically or surgically) and "spontaneous perforations" occurring before 7 days of life; *Infection*, included both early and late culture-positive, neonatal infections; *Average daily fluids*, fluid intake during first 96 hours after birth (ml/kg/day); *PDA after indomethacin treatment*, persistent ductus arteriosus patency on echocardiogram performed 24–36 hours after completing course of indomethacin; *Dopamine*, received dopamine infusion for hypotension; *Hydrocortisone-treated hypotension - "post surgical/PDA ligation"*, hypotension that was treated with hydrocortisone within 48 hours after a PDA ligation; *Hydrocortisone-treated hypotension - with serum cortisol ≤10 μg/dL*, infants who had serum cortisol ≤10 μg/dL just prior to starting hydrocortisone for hypotension

Table 2

Associations between Non-hemodynamic Risk Factors and Severe ROP - Multivariable model

Variable	Severe ROP	
	Adjusted OR (95% CI)	P-value
Gestational age	0.59 (0.42 – 0.84)	0.003
Small for gestational age	2.62 (0.79 – 8.75)	0.116
Caucasian	---	NS
Male sex	---	NS
Antenatal Betamethasone	---	NS
Preeclampsia	---	NS
Gestational Diabetes	---	NS
Chorioamnionitis	---	NS
Respiratory Distress Syndrome	---	NS
Surfactant	---	NS
RSS at 24 hours	---	NS
Bronchopulmonary Dysplasia	2.02 (0.96–4.24)	0.06
Necrotizing Enterocolitis	---	NS
Intracranial Hemorrhage (Grades 3 or 4)	---	NS
Cystic Periventricular Leukomalacia	---	NS
Infection	---	NS
Average daily fluids	1.01 (0.99–1.02)	0.12
PDA after indomethacin treatment	---	NS

The multivariable model was constructed as described in Methods. Adjusted ORs, CIs, and P-values are displayed for each of the independent variables in the model only if their p-values were <0.20. NS = p-value ≥0.20. Definitions: see Table 1 legend.

Table 3

Associations between Hemodynamic Risk Factors and Severe ROP - Multivariable model

Outcome variable	Severe ROP	
	Adjusted OR (95% CI)	P-value
Dopamine	1.9 (0.8–4.6)	0.15
Hydrocortisone-treated hypotension	7.9 (3.2–19.4)	< 0.001
Hydrocortisone start date ≤ 14 days versus control infants †	4.6 (1.5–14.3)	0.008
Hydrocortisone start date > 14 days versus control infants †	10.8 (4.1–28.7)	< 0.001
Hydrocortisone duration ≤ 4 days versus control infants §	5.5 (1.8–17.0)	0.003
Hydrocortisone duration > 4 days versus control infants §	10.1 (3.7–28.0)	< 0.001
Hydrocortisone-treated hypotension - "idiopathic"	10.1 (3.7–27.5)	< 0.001
Hydrocortisone-treated hypotension - "infection/NEC"	---	NS
Hydrocortisone-treated hypotension - "post surgical/PDA ligation"	---	NS
Hydrocortisone-treated hypotension - with serum cortisol ≤10 μg/dL *	19.1 (6.4–56.8)	< 0.001

Values represent the adjusted ORs, CIs, and P-values for each of the hemodynamic variables after they had been forced into the multivariable model displayed in Table 2. Definitions: see Table 1 legend.

† *Start date* for hydrocortisone-treated hypotension was examined as a trivariate variable: infants started on hydrocortisone ≤ 14 days after birth, infants started on hydrocortisone > 14 days after birth, and control infants who never received hydrocortisone for hypotension.

§ *Duration* of hydrocortisone treatment for hydrocortisone-treated hypotension was examined as a trivariate variable: infants who received hydrocortisone (≥ 1 mg/kg/day) for ≤ 4 days, infants who received hydrocortisone (≥ 1 mg/kg/day) for > 4 days, and control infants who never received hydrocortisone for hypotension.

* *Hydrocortisone-treated hypotension - with serum cortisol ≤10 μg/dL*: this was examined as a trivariate variable: infants with serum cortisol ≤10 μg/dL prior to hydrocortisone treatment, infants with serum cortisol ≥11 μg/dL prior to hydrocortisone treatment, and control infants who never received hydrocortisone for hypotension.