Complications associated with the current sequential pharmacological management of early postnatal hypotension in extremely premature infants

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ABSTRACT

Early postnatal hypotension in premature infants is treated with escalating doses of vasopressor-inotropes (VI), followed by hydrocortisone if VI therapy fails. The adverse effects of this standard clinical practice have not been well reported. In a retrospective case-control study, we compared the complications associated with VI and hydrocortisone (HCVI) treatments in extremely low-birth-weight infants (≤ 1000 g) with contemporaneous normotensive medication-naïve controls via standard univariate and multivariate analyses. Birth weight, gestational age, and receipt of antenatal steroids did not differ between VI ($n=74$) and control ($n=124$) groups, while the occurrence of gestational diabetes mellitus and risks for patent ductus arteriosus, intraventricular-periventricular hemorrhage, spontaneous intestinal perforation, ventriculomegaly, and bronchopulmonary dysplasia were higher in VI. Infants in the HCVI group ($n=69$) had lower birth weight, gestational age, and receipt of antenatal steroids and higher risks for intraventricular-periventricular hemorrhage, bronchopulmonary dysplasia, air leaks, and patent ductus arteriosus than controls. Whereas the occurrences of spontaneous intestinal perforation, ventriculomegaly, and maternal diabetes mellitus did not differ, that of maternal hypertension trended to be lower in HCVI recipients ($P=0.06$). In conclusion, hypotensive extremely low-birth-weight infants treated with VI or with HCVI are susceptible to intraventricular-periventricular hemorrhage, bronchopulmonary dysplasia, and patent ductus arteriosus. Furthermore, those who receive inotropes are at risk for spontaneous intestinal perforation and ventriculomegaly. Maternal diabetes mellitus increases the occurrence of hypotension, which responds to VI. Maternal hypertension does not contribute to VI responsive and tends to decrease the occurrence of VI-refractory hypotension.

KEYWORDS Adverse effects; hydrocortisone; inotropes; neonatal hypotension

Early postnatal hypotension (EPH) has been associated with mortality and long-term neurodisabilities in extremely low-birth-weight (ELBW) infants (birth weight <1000 g).^{1–7} Despite extensive research and multiple therapeutic options, there is no consensus among clinicians on the optimum pharmacological management of this morbidity.^{8–11} Recent evidence has suggested that the adverse outcomes associated with EPH may be attributable to the therapeutic interventions and not to the morbidity per se.^{4,12–15} Still, according to a recent survey, over 80% of neonatologists in practice continue to treat

EPH with medications for reasons such as lack of scientific evidence-based definitions of EPH in ELBW neonates and potential adverse effects of the morbidity. The current standard of care of hypotension in ELBW involves a regimen of volume expansion, inotropes, and hydrocortisone, instituted in a sequential and escalating order until the desired improvement in blood pressure is achieved. In this study, we investigated the complications associated with this management regimen for EPH in ELBW infants by comparing them to a baseline group of normotensive medication-naïve controls.

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METHODS

This retrospective, case-control single-center study included all inborn and outborn non-anomalous ELBW infants admitted to the neonatal intensive care unit of the University of Maryland Hospital, Baltimore, between January 2003 and December 2009, as identified from the institutional database. Those who died or were transferred out during the first 24 hours of life were excluded. The study was approved by the institutional review board.

The definition of hypotension utilized for treatment was a decrease in the mean arterial blood pressure below the numerical value of the gestational age, associated with oxygen desaturation.³ Arterial blood pressure was continually measured from an indwelling peripheral or umbilical arterial catheter connected to a transducer monitoring system zeroed at the midaxillary line (Critical Care Systems Transpac IV, Abbott Australasia, Kurnell, New South Wales, Australia). The wave form and numerical values of mean blood pressure were recorded (Agilent CMS 2000) and continually displayed on a bedside monitor (Viridia CMS 2000 series). The same bedside monitor was also used to measure and display cardiorespiratory data, including arterial oxygen saturation, which was continuously monitored via a neonatal sensor. Peripheral blood pressure was obtained by the oscillometric technique (Dinamap) in infants without an indwelling catheter. An indwelling arterial catheter was secured within 6 hours if limb manometry suggested the diagnosis of hypotension. All infants were initially treated with normal saline for volume expansion; if that failed, inotropes were initiated, first as dopamine and then as dobutamine if a desirable response was not achieved. Hydrocortisone was used for refractory hypotension, which was defined as the inability to maintain acceptable mean blood pressure despite treatment with maximum doses of dopamine, dobutamine, and/or epinephrine, in addition to volume expansion. The maximum doses of dopamine and dobutamine used were 20 mcg/kg/min. Epinephrine was used in a dose of 0.05 to 1 mcg/kg/min. Normal saline as an intravenous volume expander was given as aliquots of 10 mL/kg. There was no predefined number of boluses to be used before vasopressors were introduced. Hydrocortisone was given intravenously in a dose of 2 mg/kg/day divided into three doses for 3 to 5 days.¹⁶ The diagnosis of hypotension and decisions to give volume, inotropes, or hydrocortisone were made based on team members' clinical judgment. Infants who responded to volume and did not require inotropes or who did not have an indwelling arterial catheter were excluded from the study.

The following maternal variables were studied: clinical or histological chorioamnionitis, diabetes mellitus, hypertension, receipt of antenatal steroids, and history of substance abuse, including cocaine, narcotics, nicotine, and cannabis. Neonatal data were collected for the first 14 days after birth and included gestational age; birth weight; sex; race; vaginal or cesarean section delivery; Apgar scores at 1 and 5 minutes of life; highest mean airway pressure and fractional inspired

oxygen on postnatal days of life 1 and 7; receipt of surfactant in doses >1; patent ductus arteriosus as diagnosed by echocardiogram and treated medically or surgically; air leak syndrome including pneumothorax, pneumomediastinum, and pneumopericardium; necrotizing enterocolitis; spontaneous intestinal perforation; and intraventricular-periventricular hemorrhage of any grade. The diagnosis of necrotizing enterocolitis was made if the infant presented with stage IIA or higher of the modified Bell's criteria. The diagnosis of spontaneous intestinal perforation was made with radiologic findings of pneumoperitoneum in the absence of pneumatosis intestinalis and portal venous air, further confirmed by the surgical findings of an isolated bowel perforation with an otherwise visually and histopathologically normal bowel. The neonatal outcome variables included in the study were periventricular leukomalacia, ventriculomegaly, death before discharge, and oxygen dependence at 36 postmenstrual weeks of life (bronchopulmonary dysplasia).

Data were analyzed under three groups: ELBW infants who received hydrocortisone after the failure of vasopressor/inotrope therapy (HCVI), those who were treated with and responded to vasopressor/inotropic drugs (VI), and those who were normotensive (controls). Infants in the HCVI and VI groups were compared with controls. Student's *t*, chi square, and Fisher's exact tests were performed for univariate analyses, whereas linear regression and multiple logistic regression were performed for multivariate analyses after controlling for confounding variables. Odds ratios with 95% confidence intervals were calculated for risk assessment. Statistical analysis was done by two biostatisticians independently using the software package SPSS version 17. *P* values < 0.05 were considered significant.

RESULTS

The total number of ELBW infants delivered during the study period was 314, 47 of whom were excluded for death within 24 hours of life (11), incomplete data (27), and presence of congenital anomalies including hydrops fetalis (9). Among the 267 infants included in the final analysis, 143 were hypotensive; 69 received hydrocortisone after failure of VI (HCVI) and the remainder (*n* = 74) were treated with and responded to inotropes after the failure of volume expansion therapy (VI). A total of 124 normotensive infants served as controls. Only one infant received epinephrine for the duration of <2 hours, and the others were treated with dopamine and dobutamine.

The results of univariate analysis of infants in the three groups are presented in *Tables 1 and 2*. Birth weight, gestational age, receipt of antenatal steroids, mean airway pressure, and fractional inspired oxygen on day 1 did not differ between the VI and control infants, whereas occurrences of bronchopulmonary dysplasia, medically treated patent ductus arteriosus, intraventricular-periventricular hemorrhage, spontaneous intestinal perforation, ventriculomegaly, and gestational diabetes mellitus were higher in the VI group. In the

Table 1. Univariate analysis of the clinical characteristics of infants in the three groups via *t* test

Variables	Mean (SD)			P value	
	Control (<i>n</i> = 124)	VI (<i>n</i> = 74)	HCVI (<i>n</i> = 69)	VI vs control	HCVI vs control
Gestational age (weeks)	26.1 (2.5)	26.1 (1.2)	25.1 (1.3)	0.7	0.01
Apgar score at 1 minute	4.7 (2.8)	4.06 (2.4)	3.8 (2.4)	0.08	0.03
Apgar score at 5 minutes	6.2 (2.9)	6.3 (2.2)	6.4 (1.2)	0.8	0.7
Birth weight (g)	744.5 (186.2)	734.2 (141.37)	676.1 (121.4)	0.6	0.002
Maximum MAP (cm/H ₂ O): Day 1	8.1 (2.4)	8 (2.1)	8.3 (1.7)	0.7	0.5
Maximum MAP (cm/H ₂ O): Day 7	5.8 (1.2)	6.9 (1.8)	8.1 (1.8)	0.01	0.001
Maximum FiO ₂ (%): Day 1	42.1 (21.2)	44.1 (22.3)	46.9 (22.2)	0.6	0.2
Maximum FiO ₂ (%): Day 7	28.3 (13.2)	31.6 (13.7)	48.2 (27)	0.2	0.01
Mean BP (mm Hg): Day 3	36.6 (6.3)	33 (5.5)	31.4 (5)	0.05	0.01

BP indicates blood pressure; FiO₂, fractional inspired oxygen; HCVI, vasopressor-inotropes and hydrocortisone; MAP, mean airway pressure; VI, vasopressor-inotropes.

Table 2. Univariate analysis of the clinical characteristics and complications in infants in the three groups utilizing chi square and Fisher's exact tests

Variable	N (%)			P value	
	Control (<i>n</i> = 124)	VI (<i>n</i> = 74)	HCVI (<i>n</i> = 69)	VI vs control	HCVI vs control
Antenatal steroids	79 (64%)	50 (68%)	37 (54%)	0.8	0.03
Cesarean section	59 (48%)	44 (59%)	43 (62%)	0.1	0.07
Male	77 (62%)	43 (58%)	37 (54%)	0.6	0.2
Surfactant	34 (27%)	36 (49%)	30 (43%)	0.02	0.02
PDA	29 (23%)	38 (51%)	43 (62%)	0.001	0.01
PDA ligation	5 (4%)	6 (8%)	12 (17%)	0.2	0.001
IVH	21 (17%)	28 (38%)	39 (56%)	0.007	0.01
Air leak syndrome	4 (3%)	7 (9%)	11 (16%)	0.06	0.001
Necrotizing enterocolitis	13 (10%)	10 (14%)	13 (19%)	0.8	0.5
Spontaneous intestinal perforation	2 (2%)	7 (9%)	2 (3%)	0.01	0.5
Oxygen at day 28	49 (40%)	42 (57%)	41 (59%)	0.01	0.01
Oxygen at 36 weeks' gestation	16 (13%)	24 (32%)	22 (33%)	0.001	0.001
Ventriculomegaly	6 (5%)	11 (16%)	5 (7%)	0.02	0.6
Death	23 (19%)	16 (22%)	20 (29%)	0.6	0.1
Chorioamnionitis	10 (8%)	7 (9%)	8 (12%)	0.7	0.9
Prolonged rupture of membrane	17 (14%)	17 (23%)	15 (22%)	0.09	0.1
Maternal hypertension	14 (11%)	10 (14%)	4 (6%)	0.9	0.06
Maternal drug abuse	13 (10%)	9 (12%)	4 (6%)	0.7	0.2
Maternal diabetes mellitus	5 (4%)	13 (18%)	4 (6%)	0.01	0.9

HCVI indicates vasopressor-inotropes and hydrocortisone; IVH, intraventricular periventricular hemorrhage; PDA, patent ductus arteriosus; VI, vasopressor-inotropes.

Table 3. Multivariate analysis and risk assessment of morbidities in hypotensive infants who received VI or HCVI

Variable	VI			HCVI		
	OR	95% CI	P	OR	95% CI	P
PDA (all)	3.4	1.8–6.4	0.001	5.4	2.8–10.2	0.01
PDA with ligation	2.1	0.6–7.1	0.2	5	1.6–14.9	0.001
Air leak syndrome	3.1	0.8–11	0.07	5.6	1.7–18.6	0.001
IVH	2.8	1.3–6.2	0.007	6	2.7–13.1	0.01
Spontaneous intestinal perforation	6.3	1.2–31.5	0.01	1.8	0.25–13.2	0.5
Oxygen at 36 weeks' gestation	3.2	1.6–6.7	0.001	3.1	1.5–6.4	0.001
Ventriculomegaly	3.8	1.1–13	0.02	1.3	0.3–5.7	0.6
Maternal diabetes mellitus	3.6	1.2–10.8	0.02	1	0.2–4	0.9
Maternal hypertension	0.9	0.38–2.3	0.9	0.3	0.1–1.1	0.06

CI indicates confidence interval; HCVI, vasopressor-inotropes and hydrocortisone; IVH, intraventricular periventricular hemorrhage; OR, odds ratio; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation; VI, vasopressor-inotropes.

Figure 1. Complications associated with nonrefractory hypotension treated with vasopressors/inotropes (VI) and refractory hypotension treated with inotropes and hydrocortisone (HC). Oxygen dependence at 36 postmenstrual ages is presented as bronchopulmonary dysplasia. * $P < 0.05$ for HC group vs control; • $P < 0.05$ for VI group compared with control.

multivariate analysis (Table 3, Figures 1 and 2a), infants in the VI group were at increased risk for patent ductus arteriosus, intraventricular-periventricular hemorrhage, spontaneous intestinal perforation, ventriculomegaly, bronchopulmonary dysplasia, and for receiving more than one dose of surfactant. More infants in this group were exposed to gestation-associated diabetes mellitus in utero compared with controls. Infants in the HCVI group had lower birth weight and gestational age and were less exposed to antenatal steroids compared to controls. The occurrences of intraventricular-periventricular hemorrhage, air leaks, medically treated patent ductus arteriosus, patent ductus arteriosus requiring surgical ligation, and bronchopulmonary dysplasia were higher in the HCVI infants. All of these differences remained significant after controlling for antenatal steroids, gestational age, and

Figure 2. Forest plot showing complications associated with (a) nonrefractory hypotension and (b) refractory hypotension in extremely low-birth-weight infants compared with normotensive controls. CI indicates confidence interval; GA, gestational age (weeks); IVH, intraventricular periventricular hemorrhage; O₂, oxygen; OR, odds ratio; PDA, patent ductus arteriosus; SIP, spontaneous intestinal perforation.

birth weight. Infants in the HCVI group were at higher risk for intraventricular-periventricular hemorrhage, bronchopulmonary dysplasia, air leaks, patent ductus arteriosus requiring surgical ligation, and receipt of multiple doses of surfactant (Table 3, Figures 1 and 2b). The occurrences of spontaneous intestinal perforation, necrotizing enterocolitis, and ventriculomegaly did not differ, and there was no gender or mortality difference between either group and the control group. According to a post hoc analysis, HCVI recipients were significantly smaller ($P = 0.03$), less mature ($P = 0.005$), and less exposed to antenatal steroids ($P = 0.03$), and they displayed more severe pulmonary disease ($P = 0.01$) compared to the VI recipients.

DISCUSSION

This study suggests that the current modality of pharmacological treatment in EPH is associated with significant complications, such as intraventricular-periventricular hemorrhage, patent ductus arteriosus, and bronchopulmonary dysplasia in ELBW infants, independent of gestational age, birth weight, and receipt of antenatal steroids when compared with those who are normotensive and medication naïve. In addition, the use of inotropes was found to be associated with ventriculomegaly and spontaneous intestinal perforation, whereas infants treated with hydrocortisone for vasopressor/inotrope-refractory hypotension did not exhibit such risks despite being more premature and less exposed to antenatal steroids. It was also noted that maternal diabetes mellitus increased the occurrence of hypotension, which ameliorated with VI, whereas there was a trend for maternal hypertension to occur less frequently in the recipients of hydrocortisone ($P = 0.06$). Even though there is ample literature on the adverse effects and complications of hypotension and its medicinal management in preterm infants, to the best of our knowledge, this is the first report that directly addresses and documents the results of the contemporary

standard bedside pharmacological interventions in this critical morbidity of extremely preterm neonates. Because hypotension and volume therapy were common to both treated groups, the analyses of drug effects were not confounded by their presence.

Inotrope therapy has been associated with hearing deficits, intraventricular hemorrhage, and abnormal cranial ultrasound findings when used for EPH in preterm infants,^{3–7} whereas hydrocortisone is documented to be associated with intraventricular-periventricular hemorrhage, periventricular leukomalacia, death, cerebral palsy, and poor neurodevelopment.^{4,8} The higher occurrence of spontaneous intestinal perforation and ventriculomegaly in VI-treated infants compared to the HCVI group, although counterintuitive, raises additional concerns about the safety of this modality of treatment. It is likely that the hypotensive infants who developed spontaneous intestinal perforation and ventriculomegaly responded to VI therapy and did not reach the severity to require additional hydrocortisone. The total days on VI drugs did not differ between the two groups (HCVI vs VI = 8 ± 6 and 5 ± 3 days as mean and standard deviation, $P = 0.09$), eliminating this variable as a confounder.

Spontaneous intestinal perforation and ventriculomegaly have implications for long-term neurodisabilities and gastrointestinal failure. Prematurity and postnatal hydrocortisone exposure are the two most important known risk factors for spontaneous intestinal perforation. There is no evidence that the severity of respiratory distress syndrome during the first week of life is a risk factor.^{17–20} Drugs such as antenatal steroids and postnatal indomethacin are other factors implicated in its pathogenesis.^{17–20} Ahmad et al reported an association of dopamine, but not dobutamine, with spontaneous intestinal perforation.¹⁹ Pathophysiologically, it may be reasoned that the dose, drug, and maturation-dependent vasoconstrictive effects of inotropes on regional intestinal blood flow lead to a noninflammatory vascular compromise of the muscular, mucosal, and submucosal walls of the gastrointestinal tract and trigger spontaneous intestinal perforation.^{21–23} Ventriculomegaly is a multifactorial chronic process, which is associated with birth weight, gestational age, sepsis, intraventricular-periventricular hemorrhage, and bronchopulmonary dysplasia but not with the acuity of pulmonary disease during the first week of life.²⁴ Ventriculomegaly is thought to be due to a cytokine-induced inflammatory neuronal and white matter injury in conditions of sepsis, hypoxia, and ischemia.^{25–28}

The vasoconstrictive effects of inotropic drugs could worsen the tenuous hypoxia-hypoperfusion status of the periventricular areas of the immature brain and result in glutamate- and free radical-induced damage to the preoligodendrocytes, which are the precursors of oligodendrocytes that eventually form the white matter.^{26–28} In response to intrauterine infection, cytokines released by the fetoplacental unit cross the blood-brain barrier and activate microglia, which in turn release products that impair preoligodendrocytes.^{26,27} Endogenous glucocorticoids play major roles in the control of

cytokine-mediated pathologies by inhibiting the synthesis of tumor necrosis factor, interleukin-1, interleukin-6, and arachidonic acid metabolites and inducing nitric oxide synthase.²⁹ Corticoids counter the untoward effects of cytokines and hemodynamic shock on cellular toxicity.²⁹ By virtue of such properties, hydrocortisone may improve the inflammatory process and effectively reduce cytokine- and hypoperfusion-induced cellular and white matter injury in sick ELBW infants. ELBW infants are known to be cortisol deficient at birth,¹ and hydrocortisone might act as the specific drug for its physiological replenishment in EPH in ELBW neonates. Hydrocortisone is evidenced to be as effective as inotropes in improving blood pressure in premature infants.^{16,30,31}

The effects of gestation-associated maternal morbidities on EPH in ELBW are not well studied. We noted maternal diabetes mellitus to be a risk factor for VI responsive, and maternal hypertension decreased the risk for VI-refractory hypotension. The mechanisms of these phenomena are unclear and can only be speculated. Infants exposed to gestation-associated diabetes mellitus in utero, although susceptible to hypotension, appeared to sustain a positive response to inotropes and not require hydrocortisone. Fetal insulin functions as a growth hormone, which promotes cellular hypertrophy and hyperplasia but resists their differentiation into specialized tissues that control various system organ functions. The episodic fetal hyperinsulinemia in gestation-associated diabetes mellitus may lead to a deficiency in development of the systemic blood pressure control mechanism. Fetal stress and hypoxia caused by maternal hypertension might induce endogenous corticosteroids and catecholamines, thereby enhancing maturation of blood pressure regulation and control. The effects of maternal hypertension or its medications on fetal blood pressure are not well studied.^{32–34}

A lack of equipoise among physicians and parents limits the feasibility of prospective controlled trials in EPH of ELBW neonates. Currently, neonatologists do not have a scientific evidence-backed pathophysiological definition of hypotension in preterm infants for initiating medicinal therapy. For these reasons, there is skepticism about the validity of studies on EPH and their clinical applicability, and physicians find the suggestion of “permissive hypotension” and restricted use of medications in EPH hard to implement in clinical practice. The significant adverse effects of the current pharmacological management of EPH in ELBW infants, as identified in our study, underscore the need for additional information on this critical morbidity. Investigating the pathophysiological effects of maternal diabetes mellitus and hypertension on fetal blood pressure might provide information that could help in understanding the pathogenesis and management of EPH in extremely premature neonates in the future.

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