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Vasopressin for Refractory Hypotension in Extremely Low Birth Weight Infants

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Abstract

Intravenous vasopressin at 0.01 to 0.04 units/kg/h increased median mean blood pressure from 26 mm Hg (range 18-44) to 41 mm Hg (range 17-90) by 12 hours of infusion (P = .002) and allowed weaning of catecholamines in a group of extremely low birth weight infants with refractory hypotension.

Among extremely low birth weight infants (ELBW infants < 1000 g birth weight), sepsis remains an important cause of illness and death. Septic shock may become unresponsive to conventional management with catecholamines and hydrocortisone. Treatment with vasopressin effectively restored blood pressure while allowing for a reduction of doses of catecholamines in patient s with septic shock.[1-4] Reports of vasopressin use in infants with hypotension are scarce.[5,6]

Methods

We identified all ELBW infants born at the Duke University between January 2005 and July 2007 treated for ≥1 hour with vasopressin. This study was approved by the Duke International Review Board. Acceptable mean blood pressure (MBP) was defined as >10th percentile for gestational and postnatal age.[7] Hydrocortisone (2 to 4 mg/kg/day) was used for hypotension unresponsive to catecholamines. Refractory hypotension was defined as the inability to maintain acceptable MBP despite treatment with dopamine, epinephrine, and hydrocortisone. Presumed sepsis was defined as circulatory compromise with negative cultures and concurrent antimicrobial treatment. The diagnosis of necrotizing enterocolitis (NEC) was made if the infant was ≥ stage IIA of the modified Bell's criteria.[8]

Data Collection

Hemodynamic variables and doses of catecholamines were recorded at baseline (before vasopressin infusion) and at 1, 6, and 12 hours after initiation of vasopressin. Early deaths were defined as those occurring during or within 72 hours of vasopressin infusion and late deaths were those occurring 72 hours after the end of the infusion.

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The authors declare no conflicts of interest.

Vasopressin (Abraxis Pharmaceutical, Schaumburg, Illinois) dosing was administered at 0.01 to 0.04 units/kg/h (0.00017 to 0.0007 units/kg/min).[1,5,9] Vasopressin was administered through central or midline venous catheters, at the discretion of the bedside physician for refractory hypotension.

Clinical variables at baseline were compared with values at 12 hours after initiation of vasopressin infusion. Nonparametric tests were used and intragroup comparisons were performed with the Wilcoxon signed rank test. A 2-sided *P* value <.05 was considered statistically significant. Stata 9.0 (Stata Corp., College Station, Texas) was used for statistical analyses.

Results

We identified 33 separate vasopressin infusions in 20 infants with a median gestational age at birth of 25 weeks (range 23-27) and a median birth weight of 680 g (400-980). Treatment with vasopressin began at a median age of 10 postnatal days and lasted a median of 20 hours. The vasopressin dose used was 0.01 to 0.04 units/kg/h, except for one infant who received 0.08 units/kg/h for 1 hour. Diagnoses at the start of vasopressin infusions were culture confirmed sepsis (n = 14), presumed sepsis (n = 14), and NEC (n = 5) (Table). All infants were treated with dopamine and hydrocortisone before beginning the vasopressin infusions. One vasopressin infusion started before epinephrine use.

Median MBP increased from 26 mm Hg (range 18-44) at baseline to 41 mm Hg (17-90) by 12 hours of vasopressin infusion (*P* = .002) (Figure). Mean dopamine dose decreased from 20 μg/kg/min (SD ± 2.6) at baseline to 13 μg/kg/min (±8.6) after 12 hours of vasopressin infusion (*P* = .006). Mean epinephrine dose decreased from 0.10 μg/kg/min (±0.07) at baseline to 0.05 μg/kg/min (±0.07) after 12 hours of vasopressin infusion (*P* = .04). Median heart rate was 174 beats/min (range 120–207) at baseline versus 168 beats/min (145-216) after 12 hours of vasopressin infusion (*P* = .45).

Median urine output was 3.7 mL/kg/h at baseline and 3.0 mL/kg/h after 12 hours of vasopressin infusion (*P* = .36). Median serum pH was 7.24 at baseline and 7.33 after 12 hours of vasopressin infusion (*P* = .58). Median serum lactate was 4.2 mmol/L at baseline and 4.1 mmol/L during vasopressin infusion (*P* = .76). Median serum sodium concentrations remained stable, 133 mmol/L at baseline versus 131 mmol/L during the infusion (*P* = .54).

There were 10 (50%) early deaths and 3 (15%) late deaths. Causes of death in the early death group included NEC (Table, infants 4 and 13), presumed sepsis (n = 3), and confirmed sepsis (n = 5). In the late death group, 2 infants died of NEC (Table, infants 3 and 11) and another of *Escherichia coli* meningitis (Table, infant 17).

Discussion

Vasopressin at doses of 0.01 to 0.04 units/kg/h increased MBP in this group of critically ill ELBW infants and allowed for a decrease of catecholamine dosages. The increase in MBP could reflect improved vasopressin levels. In preterm infants with low blood pressure, plasma vasopressin levels may be consistent with relative vasopressin deficiency in shock conditions.[10,11]

Splanchnic hypoperfusion is a potential complication of vasopressin, particularly concerning in ELBW infants. Meyer et al reported an infant that received 0.36 units/kg/h of vasopressin was found at autopsy to have liver necrosis.[6] In our case series, the diagnosis of NEC was made prior to the initiation of vasopressin in 3/4 (75%) infants who died of NEC (Table,

infants 4, 11, and 13). However, the possibility exists that treatment with vasopressin could worsen splanchnic perfusion and negatively impact the outcome of these infants.

Intraventricular hemorrhage, possibly multifactorial in origin, was diagnosed in 5/9 (55%) infants who received vasopressin in the first 3 days of life. None of the patients had evidence of ischemic complications of the limbs.

The early mortality rate was 50% in these critically ill ELBW infants. In a review of vasopressin use in infants and children with shock, the early mortality rate was 52/109 (48%).[12] The issue of timing of initiation of vasopressin relative to the onset of sepsis may be important, as suggested in a recent adult randomized trial, where the mortality rate was lower among patients with less severe septic shock who received vasopressin compared with norepinephrine (26% vs 36%, $P = .05$).[4] Further research evaluating the use of vasopressin in ELBW infants with refractory hypotension is needed to determine the pharmacokinetics, timing of treatment, efficacy, and side effects of vasopressin.

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Glossary

ELBW	Extremely low birth weight
MBP	Mean blood pressure
NEC	Necrotizing enterocolitis

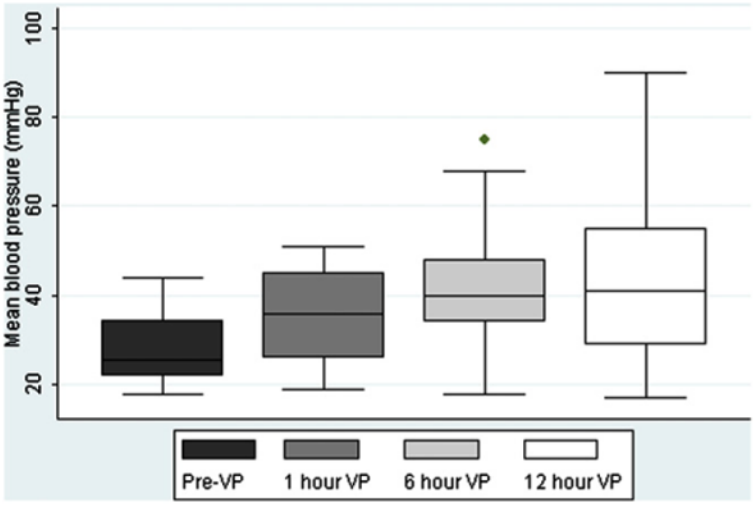

Figure.

Median MBP increased from 26 mm Hg (range 18-44) at baseline to 41 mm Hg (range 17-90) at 12 hours of vasopressin infusion (*P* = .002). Surviving infants included at each vasopressin infusion time (*n*): Pre VP (baseline) (n = 20), 6 hours (n = 18), 12 hours (n = 16).

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Table

Clinical details

Infant	Weight (g)	GA	Diagnosis	Age at VP infusions (days)	Duration of VP infusions (hours)	Outcome
1	580	26	Presumed sepsis	2	5	Survived
2	540	23	Presumed sepsis	1	9	Survived
3	610	24	Presumed sepsis	1	13	
			E Coli sepsis	32	26	Late death
4	400	24	NEC	10	37	Early death
5	600	26	Presumed sepsis	12	12	Survived
6	840	26	NEC	14	10	Survived
7	820	25	NEC	43	42	
			NEC	51	11	
			Enterococcus sepsis	240	10	Early death
8	507	26	CoNS sepsis	13	3	Survived
9	656	27	Presumed sepsis	1	70	
			Presumed sepsis	6	26	Early death
10	700	23	Presumed sepsis	2	20	
			Presumed sepsis	3	27	Early death
11	980	26	NEC	26	62	Late death
12	710	27	Presumed sepsis	2	126	
			CoNS sepsis	29	171	
			Presumed sepsis	44	14	
			Presumed sepsis	45	33	Early death
13	840	26	NEC	12	13	Early death
14	750	25	*E. coli* sepsis	1	2	Early death
15	660	24	*Enterobacter* sepsis	9	3	
			Enterobacter sepsis	10	7	Early death
16	770	27	Presumed sepsis	22	22	
			Presumed sepsis	24	2	Survived
17	710	24	GBS**	1	25	
			GBS/Candida sepsis	3	1	
			GBS/Candida sepsis	3	3	Late death

Infant	Weight (g)	GA	Diagnosis	Age at VP infusions (days)	Duration of VP infusions (hours)	Outcome
18	860	24	MRSA*** sepsis	1	35	
				3	49	Early death
19	630	23	CoNS sepsis	12	6	Survived
20	550	24	CoNS sepsis	15	11	Early death

GA, Gestational age; *VP*, vasopressin; *CoNS*, coagulase-negative *Staphylococcus; GBS*, group B *Streptococcus; MRSA*, methicillin-resistant *Staphylococcus aureus*.