JPPT | Clinical Investigation

Use of Vasopressin in Neonatal Intensive Care Unit Patients With Hypotension

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OBJECTIVE To evaluate the safety and efficacy of vasopressin for the treatment of hypotension in patients admitted to neonatal intensive care units (NICUs).

METHODS Vasopressin use in 69 infants admitted to our NICU between 2011 and 2014 was examined. Data evaluated included demographics; serum creatinine, sodium, and lactate concentrations; urine output; and systolic, diastolic, and mean blood pressures (BPs). Parameters prior to vasopressin use were compared to those at maximum dose.

RESULTS Vasopressin use was associated with increased urine output ($p < 0.05$), and increased systolic ($p < 0.0005$), diastolic ($p < 0.01$), and mean ($p < 0.001$) BP. There were no differences in sodium or lactate concentrations before vs during infusion; vasopressin use was not associated with hyponatremia (sodium < 130 mEq/L) at the maximum dose.

CONCLUSIONS Vasopressin for the treatment of neonatal hypotension appears safe and was efficacious in raising BP. These data suggest that vasopressin could be considered a viable option in the treatment regimen in hypotensive infants in the NICU.

ABBREVIATIONS BP, blood pressure; ELBW, extremely low birth weight; IUGR, intrauterine growth restriction; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; VLBW, very low birth weight

KEYWORDS blood pressure; neonates; preterm; vasopressin; vasopressors

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Introduction

Neonatal hypotension is frequently diagnosed in patients admitted to the neonatal intensive care unit (NICU); preterm and very low-birth-weight (VLBW, birth weight < 1500 g) infants are particularly vulnerable.[1] Hypotension is associated with increased risk of intraventricular hemorrhage, neurodevelopmental disabilities, and death.[2] The most commonly used medication for the treatment of neonatal hypotension is dopamine,[3] which exhibits dose-dependent effects including vasoconstriction and positive inotropy and chronotropy.[4] We showed that dopamine use has declined and vasopressin use has increased for the treatment of neonatal hypotension during the last decade.[3] Vasopressin exerts its effects through vascular V1 receptors (that increase arterial vasoconstriction) and renal tubular V2 receptors (that increase water reabsorption).[5] In our randomized, controlled pilot trial of vasopressin vs dopamine as first-line therapy for hypotension in extremely low-birth-weight (ELBW, birth weight < 1000 g) infants, we observed that vasopressin was as effective in raising blood pressure (BP) as dopamine.[6] Others have also shown that vasopressin increased BP and was associated with increased urine output in ELBW infants with refractory hypotension.[7] In infants with congenital diaphragmatic hernia and refractory hypotension, vasopressin improved systemic hemodynamics without compromise to the pulmonary vasculature.[8]

Because vasopressin has minimal inotropic and chronotropic effects[5] and may cause pulmonary vasodilation,[8–10] it is potentially preferable to dopamine for treatment of neonatal hypotension. However, the limited number of vasopressin studies in infants and its theoretical side effects have hindered its use in the NICU. To examine the safety and efficacy of vasopressin use in hypotensive infants, we performed a retrospective chart review of patients admitted to our NICU.

Materials and Methods

The study was approved by the Baylor College of Medicine Institutional Review Board and a waiver of informed consent was obtained. Patient demographics, primary underlying diagnoses, and all medications used for the treatment of hypotension were collected from the electronic medical record (EPIC, Madison, WI) and the pharmacy database. The pharmacy database was queried for infants (inborn and outborn) admitted to the NICU between January 1, 2011, and December 31, 2014, who received intravenous vasopressin infu-

Table 1. Patient Characteristics

Characteristic	Entire Cohort (N = 69)	VLBW Infants (n = 21)
Birth weight, g*	2220 ± 1275	768 ± 279
Gestational age, wk*	33.4 ± 6.0	26 ± 2.4
Sex, male	40 (58)	14 (67)
Race		
White	43 (62)	16 (76)
Black	17 (25)	3 (14)
Other	4 (6)	0
Hispanic/Latino	25 (36)	9 (43)
Inborn	30 (44)	10 (48)
Vaginal delivery	28 (41)	7 (33)
Multiple gestation	8 (12)	8 (38)
Antenatal steroids	25 (36)	16 (76)
Intrauterine growth restriction	11 (16)	4 (19)
1-min Apgar, median (IQR)	4 (1.5, 6)	3 (1, 4)
5-min Apgar, median (IQR)	7 (5, 8)	6 (4.3, 7)
Sepsis	7 (10)	3 (14)
Initial hematocrit, %*	39.7 ± 9.4	33.2 ± 8.7
ECMO	14 (20)	0
Necrotizing enterocolitis		
Prior to vasopressin	3 (4)	2 (10)
During vasopressin	0	0
After vasopressin	2 (3)	1 (5)
Death	35 (51)	15 (71)

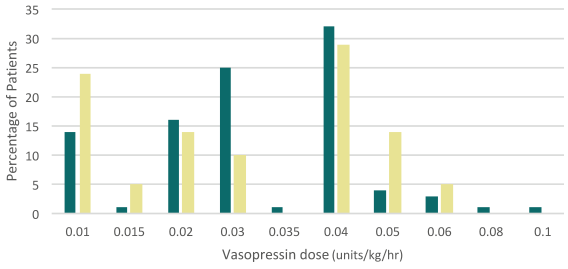
ECMO, extracorporeal membrane oxygenation; VLBW, very low birth weight
* Mean ± SD, all others n (%) unless otherwise noted.

sion during their initial hospitalization. Infants were excluded if medication administration details, such as starting time or starting dose, were unknown; if duration of administration was <4 hours; or if administration was begun prior to transfer to the NICU. Additionally, for patients with multiple courses of vasopressin, only the first administration was evaluated. Subjects with congenital heart disease were excluded from the VLBW infant group (to have a more homogeneous group of hypotensive premature infants) but were included in the overall study sample.

Data obtained from the electronic medical record included birth weight, gestational age, sex, race, and ethnicity; prenatal factors, such as receipt of antenatal steroids, multiple gestation, and intrauterine growth restriction (IUGR) status; delivery method; primary diagnoses; Apgar scores; serum creatinine, sodium, glucose, and lactate concentrations; urine output; systolic, diastolic, and mean BP; and receipt of extracorporeal membrane oxygenation. Hematocrit, presence of sepsis within 72 hours prior to vasopressin administration, and incidence of necrotizing enterocolitis (NEC, stage IIa or greater[11]) before, during, or after vasopressin use were also noted. Blood pressure data were obtained from invasive arterial catheters when present.

Statistical analyses were performed by using SPSS (version 22, IBM, Armonk, NY). Descriptive statistics were used to characterize the patient population (mean and SD or median and IQR). For the analysis, 2 groups were identified and analyzed separately: all infants and the subgroup of VLBW infants. The measurements examined at baseline (prior to vasopressin) and maximum dose included serum creatinine, sodium, and lactate concentrations; urine output; and systolic, diastolic, and mean BP. In addition, we analyzed each group for the incidence of hyponatremia (defined as sodium < 130 mEq/L) prior to and during vasopressin administration. Continuous data were analyzed by using a related-samples Wilcoxon signed rank test, and categorical data were analyzed by using a related-samples McNemar test. The 69 study patients provided 80% statistical power to detect ($\alpha = 0.05$) an effect size (mean change/SD of change) of 0.52 in initial biomarker levels compared to biomarker levels at maximum dose,

Figure 1. Maximum dose of vasopressin.



VLBW, very low birth weight.
Cohort; VLBW

after considering that the Wilcoxon signed rank test could require a 15% larger sample size as compared to the paired *t* test.[12] This is considered to be a "medium" effect size according to Cohen's conventional criteria.[13]

Results

Entire Cohort. In total, 69 patients met study inclusion criteria (58% male). Mean gestational age at birth was 33.4 ± 6 weeks (range, 22.7–41.9 weeks) and mean birth weight was 2220 ± 1275 g (range, 340–5160 g). Patient characteristics are shown in Table 1. The initial vasopressin infusion rate was 0.014 ± 0.007 units/kg/hr and the maximum dose was 0.032 ± 0.016 units/kg/hr (Figure 1). Average duration of vasopressin infusion was 64.6 ± 4.2 hours. None of the patients developed NEC while on vasopressin and only 10% were diagnosed with sepsis within 72 hours prior to receiving vasopressin. Other clinical variables are listed in Table 2. Primary diagnoses for the entire cohort are listed in Table 3. The overall mortality rate in this cohort was high (51%, 35 of 69 patients); 17% (6 of 35 patients) of the deaths occurred while on vasopressin, and 31% (11 of 35 patients) of infants died after redirection of intensive care. Subjects were treated with 1.5 ± 0.9 other inotropic or antihypotensive medications prior to the initiation of vasopressin (Figure 2). There were no differences in sodium ($p = 0.667$) or lactate ($p = 0.658$) concentrations prior to and during maximum dose of vasopressin (Table 2). Only 1 patient had an increase in creatinine >0.5 mg/dL after starting vasopressin. In addition, there were no differences between the number of patients with hyponatremia ($p = 0.424$) prior to and during vasopressin infusion at maximum dose. Urine output ($p < 0.05$) increased and percentage change in systolic BP ($p < 0.0005$), diastolic BP ($p < 0.01$), and mean BP ($p < 0.001$) was significant at maximum dose vasopressin infusion compared to baseline.

VLBW Cohort. The largest homogeneous group of patients was VLBW infants (n = 21, 30% of the total cohort). Mean gestational age was 26.0 ± 2.4 weeks (range, 22.7–32.1 weeks) and mean birth weight was 768 ± 279 g (range, 340–1390 g). Patient characteristics are described in Table 1. The initial vasopressin infusion rate was 0.015 ± 0.008 units/kg/hr and the maximum dose was 0.03 ± 0.016 units/kg/hr. None of the patients developed NEC while on vasopressin and 14% were diagnosed with sepsis within 72 hours prior to receiving vasopressin. Other clinical variables are listed in Table 2. The mortality rate was 71% (15 of 21 patients); 27% (4 of 15 patients) of the deaths occurred while on vasopressin, and 20% of infants died after redirection of intensive care. Patients were treated with 1.9 ± 0.7 other inotropic

Table 2. Clinical Studies

Variable	Entire Cohort (N = 69)	p value	VLBW Infants (n = 21)	p value
Serum sodium, mEq/L				
Initial sodium	137.4 ± 7.8	0.667	138.6 ± 9.0	0.795
At maximum vasopressin dose	137.0 ± 8.1		138.4 ± 8.2	
Serum lactate, mmol/L				
Initial	4.8 ± 6.0	0.658	6.6 ± 6.5	0.594
At maximum vasopressin dose	5.1 ± 6.2		6.6 ± 7.3	
Urine output, mL/kg/hr				
Initial	2.2 ± 2.5	< 0.05	1.7 ± 2.7	< 0.05
At maximum vasopressin dose	3.0 ± 3.3		3.3 ± 3.9	
Percentage change in BP*				
Systolic BP*	6.9 (0, 20.7)	< 0.0005	7.3 (0, 26.8)	< 0.05
Diastolic BP*	6.7 (0, 22.2)	< 0.01	17.1 (0, 33.3)	< 0.05
Mean BP*	6.8 (0, 21.7)	< 0.001	11.5 (0, 32.9)	< 0.005

* Data presented in median (IQR), otherwise mean ± SD.

Table 3. Primary Diagnosis of Entire Cohort (N = 69)

Primary Diagnosis	n (%)
Prematurity	19 (28)
Extremely low birth weight	17
Very low birth weight	2
Congenital heart disease	12 (18)
Transposition of great arteries	4
Atrioventricular canal defect	2
DORV	1
Coarctation of aorta	1
Tetralogy of Fallot	1
Complex congenital heart disease	3
Congenital diaphragmatic hernia	11 (16)
Congenital diaphragmatic hernia + DORV	1
Persistent pulmonary hypertension of newborn	10 (15)
Hypoxic-ischemic encephalopathy	4 (6)
Hydrops fetalis	4 (6)
Herpes simplex virus sepsis	3 (4)
Other	5 (7)

DORV, double outlet right ventricle

or antihypotensive medications prior to the initiation of vasopressin (Figure 1). There were no significant differences in sodium ($p = 0.795$) or lactate ($p = 0.594$) prior to and during maximum dose of vasopressin (Table 2). In addition, there were no significant differences between the number of patients with hyponatremia ($p = 1.0$) prior to and during vasopressin infusion at maximum dose. No patients had an increase in creatinine > 0.5 mg/dL after starting vasopressin. Urine output ($p < 0.05$) increased and percentage change in systolic BP ($p < 0.05$), diastolic BP ($p < 0.05$), and mean BP ($p < 0.005$) was significant when compared between baseline and maximum dose values.

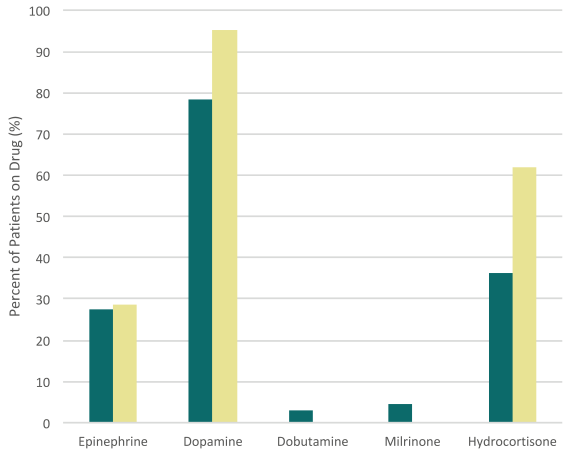
Discussion

Dopamine has historically been the initial drug of choice for the treatment of neonatal hypotension regardless of etiology. This practice, however, may not be beneficial in certain physiologic instances. For example, in patients with decreased cardiac output due to poor ventricular filling, increasing the heart rate (and thereby decreasing filling time) could have a detrimental effect of further reducing cardiac output. In addition, inotropy provided by dopamine may be unnecessary or lead to a hypercontractile state in otherwise normally functioning hearts. In these instances, using different agents as the first-line medication might be more beneficial. Vasopressin should therefore be considered as an alternative to dopamine where limited inotropy and chronotropy are desired.

The use of vasopressin has theoretical adverse effects (i.e., oliguria or anuria, hyponatremia, increased lactate concentrations, and severe vasoconstriction) that have limited its use for the treatment of hypotension in the NICU.[14,15] We therefore evaluated the efficacy and the potential adverse effects of vasopressin in our population over a 4-year period, which to our knowledge is the largest cohort of infants receiving vasopressin ever examined. Vasopressin increased systolic, diastolic, and mean BP in both cohorts. Vasopressin was also associated with increased urine output in both cohorts, which suggests an increase in renal blood flow. Importantly, hyponatremia and increased lactate concentrations were not observed after vasopressin use. Lastly, we evaluated the incidence of NEC as a surrogate marker for decreased splanchnic blood flow and observed no increased incidence during or after vasopressin administration. Thus, we observed none of the theoretical adverse effects of vasopressin that have likely limited its use as a first-line agent for the treatment of neonatal hypotension. We postulate that the lack of these adverse effects is due to the overall improvement of systemic hemodynamics that vasopressin provides.

We included all infants in the NICU who received ≥4 hours of vasopressin, which resulted in a diverse population. Since the findings were essentially equivalent between the larger diverse group and the more homogenous VLBW infant subgroup, we believe the

Figure 2. Medications used prior to vasopressin infusion.



VLBW, very low birth weight.
Overall; VLBW

beneficial effects of vasopressin for the treatment of hypotension may be independent of the underlying diagnoses. Our cohort consisted of many critically ill hypotensive infants including those with congenital heart disease, congenital diaphragmatic hernia, and extreme prematurity, of which 20% received extracorporeal membrane oxygenation. Thus, the high mortality rates observed were not surprising. Vasopressin is often added to the armamentarium of other drugs when there is refractory hypotension, as we observed, and mortality rates increase proportionately with increasing number of medications used.[6]

There are some limitations of our study. This was a single-center observational study where the prescribing of vasopressin (starting dose used, titration of the infusion, and the order of when it was begun in the treatment regimen of other agents used in treating hypotension) was at the discretion of individual attending physicians. Second, in an ideal situation, we would have had clinical and side effect parameters in all patients before and after administration of vasopressin. This was a retrospective study of clinical practice, however, and laboratory tests were not performed at prespecified times, or sometimes not performed at all. We decided *a priori* to exclude infants with congenital heart disease from the VLBW infant group, in order to obtain a homogeneous group of hypotensive infants as commonly encountered by most neonatologists. Thus, it is unclear from this study if hypotensive VLBW infants with congenital heart disease will benefit from vasopressin though they were included in the overall analysis. Further, not all patients had invasive continuous BP monitoring. We were also limited by intermittent recording of BP values in the medical record instead of having the ability to collect continuous data prospectively. Lastly, we only analyzed 4 years of data. Despite this, our study includes the largest sample size to date of NICU infants treated with vasopressin.

In conclusion, vasopressin therapy improved BP in infants with refractory hypotension and was associated with increased urine output and a lack of adverse effects (e.g., hyponatremia). This retrospective cohort review together with our pilot trial evaluating vasopressin as a first-line agent in ELBW infants illustrates that vasopressin may be considered a viable option in the treatment of neonatal hypotension. Future trials are warranted to establish pharmacokinetics of vasopressin in neonates and infants, maximum dosing range, and to further evaluate safety and efficacy in this population.

ARTICLE INFORMATION

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