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Vasopressin Improves Hemodynamic Status in Infants with Congenital Diaphragmatic Hernia

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Abstract

Objective—To assess the ability of vasopressin to stabilize hemodynamics in infants with systemic hypotension secondary to congenital diaphragmatic hernia (CDH).

Study design—A retrospective chart review was performed to identify 13 patients with CDH treated with vasopressin for refractory hypotension, to assess the effect of vasopressin on pulmonary and systemic hemodynamics and gas exchange in this setting. Data collected included demographics, respiratory support, inotropic agents, pulmonary and systemic hemodynamics, urine output, and serum and urine sodium levels during vasopressin therapy.

Results—Vasopressin therapy increased mean arterial pressure and decreased pulmonary: systemic pressure ratio, heart rate and FiO₂. In 6 of 13 patients, ECMO was no longer indicated after vasopressin treatment. Improvement in left ventricular (LV) function and oxygenation index after vasopressin initiation were associated with a decreased need for ECMO. Prolonged vasopressin treatment was associated with hyponatremia, increased urine output and increased urine sodium.

Conclusions—Vasopressin stabilized systemic hemodynamics without adverse effects on pulmonary hemodynamics in a subset of infants with CDH. Our results suggest a potential role for vasopressin therapy in patients with CDH with catecholamine resistant refractory hypotension.

Keywords

Pulmonary hypertension; shock; hyponatremia

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Despite recent improvements in the care of neonates with congenital diaphragmatic hernia (CDH), overall morbidity and mortality remain significant secondary to the development of pulmonary hypoplasia and persistent pulmonary hypertension of the newborn (PPHN) (1,2). In addition to respiratory insufficiency and PPHN, hemodynamic instability and hypotension frequently complicate the course. The etiology of hypotension in CDH is multifactorial including left ventricular (LV) systolic dysfunction with decreased LV output, decreased pulmonary blood flow with decreased LV preload, LV diastolic dysfunction with impaired LV filling secondary to interventricular septal flattening and LV compression or LV hypoplasia, and right ventricular (RV) dysfunction secondary to suprasystemic pulmonary arterial pressure (PAP) (3,4,5). In addition to ventilator support and pulmonary vasodilator therapy, cardiopulmonary support in severe CDH often requires the use of inotropic and vasopressor agents to maintain normal systemic blood pressure and reverse extra-pulmonary shunt (6,7). The most frequently used agents include catecholamines (dopamine and epinephrine), inotropes (dobutamine), and steroids (hydrocortisone). These agents are often ineffective making extracorporeal membrane oxygenation therapy (ECMO) the only therapeutic option to stabilize hemodynamics. Published studies from the CDH registry report a 27-35% (8,9) ECMO utilization rate, making alternate therapies that may be more effective in the setting of refractory hypotension essential. Two recent case reports describe the efficacy of terlipressin, an arginine vasopressin analogue, in the setting of hemodynamic instability in CDH (7,10). Based on these reports, we hypothesized that a continuous vasopressin infusion would stabilize hemodynamics and improve oxygenation without adversely affecting pulmonary vascular resistance (PVR) in the setting of CDH with refractory hypotension. We present findings from a subset of 13 neonates with CDH treated with vasopressin for refractory hypotension after meeting criteria for initiation of ECMO.

Methods

Following approval by our institutional review board, we performed a retrospective review of the medical records of all patients with CDH at Children's Hospital Colorado between 2010 and 2012 to identify patients treated with vasopressin. The aim of the study was to assess the effect of vasopressin therapy on systemic and pulmonary hemodynamics and gas exchange and to document adverse effects. Data collected include demographics, CDH severity, clinical course including ventilator strategy, the use of steroids, vasopressor and inotropic agents including doses and duration of therapy, changes in hemodynamics, frequency of ischemic events, urine output and serum and urine sodium levels during vasopressin therapy. Comparisons were made between these various measures pre and post vasopressin therapy.

At our institution, initial management of infants with CDH involves synchronized intermittent mandatory ventilation (SIMV) with volume guarantee (tidal volume 4-5ml/kg). Peak pressures greater than 25-28 cmH₂O or the inability to ventilate (pCO₂ > 65) with a respiratory rate greater than 50/minute prompts the initiation of high frequency oscillatory ventilation (HFOV). Preductal arterial access (radial or brachial) is obtained in all patients and FiO₂ is titrated based on preductal pO₂. Preductal arterial blood gasses (ABG) more accurately reflect gas exchange in the lung with postductal ABGs representing a veno-arterial admixture. Due to the high frequency of adrenal insufficiency in this population

(11), hydrocortisone (2mg/kg) is administered to all patients on admission and daily random cortisol levels are used to determine the maintenance dose required (1-2mg/kg every 8 hours). For patients with persistent hypotension, dopamine (5-20mcg/kg/min) is initiated, followed by epinephrine (0.05-0.5mcg/kg/min). Hypotension is defined as a mean arterial pressure (MAP) less than gestational age or in the case of a narrow pulse pressure, SBP < 55mmHg in a term infant. Refractory hypotension is defined as the inability to achieve or maintain goal blood pressure despite supplemental hydrocortisone and catecholamine infusions. The inability to maintain systemic blood pressure is defined by recurrent episodes of precipitous unprovoked hypotension, which frequently complicate the course in CDH. In the setting of a suprasystemic PAP, a precipitous drop in systemic blood pressure results in right to left shunting through fetal conduits leading to profound and life threatening hypoxemia. In this setting, epinephrine is often initiated prior to reaching maximum dose dopamine. If epinephrine fails to prevent these episodes patients are treated with ECMO. All 13 patients in our cohort met criteria for ECMO, however, a trial of vasopressin therapy was initiated in an attempt to achieve or maintain blood pressure goals. If vasopressin was effective in stabilizing hemodynamics, epinephrine was weaned first followed by dopamine. ECMO was initiated if refractory hypotension persisted.

Milrinone is added if there is evidence of LV systolic or diastolic dysfunction on echocardiogram. LV systolic dysfunction is determined by standard echocardiographic measures, LV diastolic dysfunction is defined by the presence of left to right shunting with evidence of systemic or suprasystemic PAP (tricuspid regurgitation (TR) jet, right to left or bidirectional DA flow). Milrinone is initiated at 0.25mcg/kg/min for 6 hours then increased to 0.5mcg/kg/min and maintained at that dose with no further titration. Indications for ECMO include, critical preductal hypoxemia (persistent preductal pO₂<40mmHg), refractory shock and/or refractory acidosis.

Statistical analysis was conducted in Prism 6.0b (by GraphPad Software, Inc. La Jolla, CA, USA). Categorical variables were compared using a Chi-Square test and continuous variables compared using a t test (normally distributed data) or Mann-Whitney two sample test (non-parametric data). Comparisons between multiple groups were made with ANOVA. Statistical analysis was performed based on available data.

Results

Forty-three infants with CDH were managed at our institution between 2010 and 2012, 13 of whom received a vasopressin infusion. Demographic data and available pre and postnatal markers of CDH severity are shown in Table I. A complete prenatal assessment of CDH severity was available for only five patients due to a >50% outborn rate. The severity of CDH was variable based on published pre and postnatal predictors. Each patient was immediately intubated, none received surfactant, and all required HFOV. All patients received hydrocortisone and dopamine (range 15-25mcg/kg/min) and 11 of 13 (85%) received epinephrine (range 0.03-0.4mcg/kg/min) prior to vasopressin initiation. All patients met criteria for ECMO cannulation.

In 11 of 13 patients, a trial of vasopressin infusion was initiated prior to ECMO therapy (range 0.0001-0.002units/kg/min, no boluses). In the remaining 2 patients (both outborn) vasopressin was initiated immediately prior to (n=1) or concurrent with ECMO cannulation (n=1). Details regarding the timing and dosage of vasopressin are shown in Table II. Following vasopressin administration, no patients required escalation of other vasopressor support and epinephrine was weaned in 6 patients (median of 0.09mcg/kg/min, range 0.02-0.2mcg/kg/min) and dopamine was weaned in 4 patients (median of 6mcg/kg/min, range 5-15mcg/kg/min). In 6 of 11 patients in whom vasopressin was not initiated concurrent with ECMO, vasopressin infusion was associated with sufficient improvement in hemodynamics that ECMO was no longer indicated. Five patients did require ECMO at an average of 9.2 hours after vasopressin therapy was initiated for preductal hypoxemia (4) and refractory acidosis (1).

12 hours following initiation of vasopressin, MAP increased from a mean of 47 ± 11.1 to $64. \pm 8.8$ ($P=0.0021$) and heart rate decreased from a mean of 172 ± 18.2 to 133 ± 17.8 ($p=0.001$) at 24 hours (Figure 1, A). Figure 1, B demonstrates similar changes in MAP and HR among those six patients who did not require ECMO therapy. Similarly, SaO₂ increased from 90.2% to 94.6% ($p = \text{NS}$) and FiO₂ decreased from $79 \pm 25.5\%$ to $41 \pm 16.9\%$ ($p=0.02$) (Figure 1, C). Figure 1, D demonstrates similar changes in these variables among those six patients who did not require ECMO. Figure 2 (available at www.jpeds.com) demonstrates changes in HR and MAP and changes in SaO₂ and FiO₂ among those 7 patients who did go on to require ECMO therapy.

Echo data for pulmonary:systemic pressure ratio was available for 8 patients; this ratio decreased by 17%, after vasopressin initiation ($p=0.07$) (Figure 3, A: available at www.jpeds.com). In the 11 patients in whom vasopressin was not initiated concurrent with ECMO, oxygenation index (OI) ($\text{FiO}_2 \times \text{Mean airway pressure} / \text{PaO}_2 \times 100$) improved by an average of 12.0 ± 18.1 . In the subset needing ECMO there was no significant change in OI (41.75 pre vs 30.20 post; $p=\text{NS}$). In the subset not needing ECMO, there was a trend towards improved OI (21.735 vs 9.32 ; $p=0.06$) (Figure 3, B).

LV dysfunction was documented in 7 of 11 infants (64%; mild=1, moderate=3, severe=3). Ten of 13 infants received a milrinone infusion at a median of 3.5 hours (range 2-84 hours) (dose 0.15-0.5 mcg/kg/min) prior to vasopressin initiation. Hemodynamic measures remained unchanged 6 hours after initiation of milrinone, with no improvement in MAP (decreased by 3.8mmHg), HR (increased by 1.6bpm), SaO₂, (decreased by 5.6%), or FiO₂ (increased by 7%). As milrinone failed to stabilize hemodynamics and gas exchange, these patients also received vasopressin therapy with no patient developing worsening LV function. LV function that remained severely depressed after initiation of vasopressin and milrinone predicted need for ECMO in 3 of 3 (100%) patients. In 4 of 7 (57%) patients, LV function improved and ECMO therapy was no longer indicated.

Hyponatremia (serum Na<134mmol/L) occurred in all patients who received >24hours of vasopressin therapy (n=6 patients, all non ECMO treated). ECMO cannulation caused sufficient stabilization of hemodynamics to allow vasopressin cessation in all patients (mean length of vasopressin therapy = 11.1 ± 5.5 hours vs 67.3 ± 41.8 hours among non ECMO;

$p < 0.01$). The median maximum dose of vasopressin in ECMO versus non-ECMO group was 0.001 units/kg/min vs. 0.00095 units/kg/min ($p = \text{NS}$). For this reason, hyponatremia complications are reported only in those 6 patients who did not require ECMO. Vasopressin increased urine output and decreased serum sodium (average nadir 117.8 mmol/L; range 111-121) (Figure 4, A and B). In all but two patients, hyponatremia resolved 6 hours following the cessation of vasopressin infusion (average $\text{Na} = 136.3$ mmol/L). All 6 patients required treatment for hyponatremia (5 received 3% NaCl infusion; 1 treated with fluid restriction). Urine sodium (Figure 4, C) was markedly elevated during days 2, 3, and 4 of vasopressin therapy but began to decrease by day 5 (average 155.2 mmol/L (range 117-214) on day 2; 77.5 mmol/L (range 52-103) on day 5). Urine sodium continued to decrease (average 51.6 mmol/L) following cessation of vasopressin infusion. Serum creatinine decreased from a mean of 0.74 ± 0.15 at vasopressin initiation to 0.53 ± 0.14 on day 1 ($p = 0.06$) and 0.34 ± 0.1 on day 3 of vasopressin therapy ($p = 0.04$) and was sustained 6 hours post vasopressin cessation (0.38 ± 0.12 ; $p < 0.01$) (Figure 4, D).

There were no adverse events due to vasopressin induced ischemia.

Discussion

Vasopressin therapy was associated with improved systemic hemodynamics and gas exchange without adverse effects on PVR in infants with CDH and refractory hypotension. Despite meeting criteria for initiation of ECMO, after initiation of vasopressin, hemodynamics and gas exchange stabilized such that 6 patients no longer met therapy criteria. These benefits were seen after hydrocortisone and milrinone failed to achieve the same end points. The fall in FiO_2 , improvement in SaO_2 , and trend towards improvement in OI after initiation of vasopressin demonstrate a favorable response and correlate well with the fall in PA:systemic blood pressure ratio. Failure of LV function and OI to improve after initiation of vasopressin predicted the need for ECMO in our patient population. This effect has been demonstrated previously in neonates with similar hemodynamic status and pulmonary hypertension (10,12,13). In addition to the cardiopulmonary effects, urine output increased after initiation of vasopressin likely secondary to stabilization of cardiopulmonary status and improved renal perfusion. Additionally, profound natriuresis occurred in all patients who received sustained vasopressin therapy with resultant hyponatremia requiring treatment with 3% NaCl in 5 of 6 patients (80%).

In the systemic circulation, vasopressin acts via V1a receptors of the smooth muscle leading to vasoconstriction of both arteries and veins (14). Work in animal models has shown that despite the vasoconstrictive effect systemically, vasopressin causes dilation of the pulmonary circulation, likely mediated via nitric oxide release from the endothelium (15,16). Vasopressin is used in the setting of cardiac arrest, sepsis, vasodilatory shock, and cardiac surgery with reported effects including improved systemic blood pressure, a decline in catecholamine requirements, and increased urine output (17,18). In studies of patients with pulmonary hypertension, vasopressin improves systemic hemodynamics without adverse effects on the pulmonary vasculature, making it an ideal agent for treatment of infants with CDH who have pulmonary hypertension and systemic hypotension (12,19).

In our series vasopressin was initiated secondary to catechoamine resistant hypotension only after all patients met criteria for initiation of ECMO. In 2 outborn patients, vasopressin stabilized hemodynamics during ECMO cannulation. In 6 of the remaining 11 patients, hemodynamics and gas exchange stabilized to the point that ECMO was no longer indicated. Five of 11 patients did go on to require ECMO for a variety of reasons. Despite improvement in OI from 36.54 to 24.44 and improved hemodynamics, one infant developed pneumopericardium, prompting initiation of ECMO. In a second case, hemodynamics and gas exchange stabilized (OI improved from 19.73 to 10.43) with vasopressin administration. However, inhaled prostacyclin therapy was started 2 hours after vasopressin initiation to treat severe pulmonary hypertension, and was associated with worsening ventilation-perfusion mismatch and preductal hypoxemia, leading to ECMO initiation. The remaining 3 patients all had evidence of severe LV dysfunction on echo and had no improvement in LV function and gas exchange following initiation of vasopressin. Failure of LV function and OI to improve 24-36 hours following initiation of vasopressin therapy was predictive of the need for ECMO in this subset of infants (3 of 3 patients) and may be important predictors of the need for ECMO in this population.

The effect of vasopressin therapy on LV function remains somewhat controversial. There is evidence in animal models that in the setting of cardiac ischemia, vasopressin can lead to worsened LV function (20,21). However, there is also data demonstrating improved LV function in the setting of cardiopulmonary bypass (22). In 4 of 7 patients with documented LV dysfunction on initial echocardiogram, the addition of vasopressin, after milrinone had already been started, lead to improvement in LV function suggesting that vasopressin may support LV function in this subset of patients.

Hyponatremia complicated the course of all patients who received sustained vasopressin therapy as has been documented previously in children after cardiac surgery (23). The associated increase in urine output and natriuresis demonstrated use has also been described previously and is thought to result from the increased renal perfusion pressure (24,25). Increased urinary sodium excretion has been described extensively in experimental animal studies (26,27,28) and is likely due to a shift from the V2 receptor mediated effects on water permeability towards the V1a natriuretic effects with higher levels of vasopressin exposure, as seen in patients receiving an exogenous vasopressin infusion (29). This description of the physiologic effects of vasopressin at different serum concentrations explains the profound natriuresis seen in our patients. Even though the mean length of vasopressin therapy differed significantly between the ECMO and non ECMO groups, the median maximum dose was not different suggesting that prolonged exposure, not dose, was likely responsible for the hyponatremia. We recommend close monitoring of serum sodium concentrations during prolonged vasopressin infusion and treatment with fluid restriction or 3%NaCl infusion when appropriate.

As with all retrospective data, these data are inherently limited and should be interpreted with caution. This subset of patients represents the sickest patients with CDH. Rates of ECMO utilization, LV dysfunction, hemodynamic instability and vasopressor use described here do not accurately represent our institutional experience. We present a subset of patients who failed other medical therapy in whom vasopressin therapy was trialed after criteria for

initiation of ECMO therapy were met. Although ECMO was no longer indicated in 6 of 13 patients, this data is not supported by randomized and controlled methodology, and this finding may be merely an association rather than a true treatment effect. For this reason we caution against widespread use of vasopressin when the above criteria are met.

The addition of a continuous infusion of vasopressin to the hemodynamically unstable infant with CDH was associated with improved gas exchange and hemodynamics without adverse effects on the pulmonary vasculature. Vasopressin therapy was also associated with significant hyponatremia with increased urine output with profound natriuresis. As a result, close monitoring of electrolytes is strongly recommended. Our data suggest a role for vasopressin in the setting of catecholamine resistant refractory hypotension and provide a rationale for a randomized trial to fully elucidate the effects of vasopressin in this unique population.

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Figure 1.

A, Among all patients (n=13), heart rate (HR) decreased and mean arterial pressure (MAP) increased after initiation of vasopressin therapy (P=0.0021). B, Same trends in HR and MAP in those patients not treated with ECMO (n=6). C, Among all patients (n=13), FiO₂ decreased significantly and SaO₂ increased with vasopressin therapy. D, Same trends in SaO₂ and FiO₂ in those patients not treated with ECMO (n=6).

Figure 2.

A, Among those patients treated with ECMO, heart rate decreased and MAP increased slightly immediately following vasopressin initiation (n=7). B, SaO2 increased slightly and FiO2 was quickly weaned to room air following initiation of ECMO therapy.

a. Pulmonary to Systemic Pressure Ratio Pre and Post Vasopressin Treatment

b. Oxygenation Index pre and post vasopressin treatment in ECMO and non ECMO groups

Figure 3.

A, Pulmonary to systemic pressure ratio pre and post vasopressin treatment (available data for 8 patients). B, Oxygenation index decreased following vasopressin administration in patients treated with ECMO (n=7) and those not treated with ECMO (n=6).

Figure 4.

A, Urine output increased significantly following initiation of vasopressin therapy in the six patients with prolonged vasopressin exposure. ($P=0.0022$). B, Serum sodium decreased following vasopressin initiation (average nadir 117.8mmol/L; range 111-121) due to excessive urinary excretion. C, Urine sodium was elevated during days 2, 3, and 4 of vasopressin therapy but decreased by day 5 and following vasopressin withdrawal. D, Serum creatinine decreased significantly by day 3 and 4 of vasopressin infusion.

Table 1

Patient demographic characteristics

Patient Number	Sex	Prenatal diagnosis?	Gestational age (weeks)	Birthweight (g)	Side of defect	Karyotype	Liver herniation	Lung to head ratio	% predicted lung volume	Total lung volume	Modified McGoon Index	Agnesis?	Patch repair
1	f	yes	37	2728	left	normal	grade 4	1.33	12%	15.2	1	no	yes
2	m	no	37	2400	right	normal	none	1.3	24%	18.4	1.2	no	yes
3	f	yes	38	3000	right	normal	grade 3	1.15	not done	not done	1.2	no	yes
4	m	yes	38	3435	left	normal	none	1.5	26%	35.3	2.1	no	no
5	f	yes	41	2890	left	normal	none	outborn	outborn	outborn	outborn	no	no
6	f	yes	38	3400	left	normal	none	outborn	outborn	outborn	outborn	no	no
7	f	yes	40	2236	left	normal	none	outborn	outborn	outborn	outborn	no	yes
8	m	yes	40	3055	left	normal	grade 1	outborn	outborn	outborn	outborn	no	yes
9	f	yes	38	3510	right	normal	grade 1	1.31	37%	39	1.2	no	no
10	f	no	38	3075	left	normal	grade 3	outborn	outborn	outborn	outborn	yes	yes
11	m	yes	38	3200	left	normal	none	outborn	outborn	outborn	outborn	no	no
12	f	yes	36	2200	left	normal	none	1.1	19.60%	19	1.2	no	yes
13	f	yes	38	3330	left	normal	grade 1	1.46	not done	not done	not done	no	yes

Table 2

Details of timing of vasopressin initiation and dosage

Patient number	Length of vasopressin administration (hrs)	Day of life at initiation	Vasopressin dose range (unites/kg/min)	# of times vasopressin restarted after wean initiated
1	4	2	0.00200	1
2	6	1	0.0005-0.0008	1
3	15	1	0.0004-0.0008	2
4	9	2	0.005	0
5	22	1	0.0002-0.001	0
6	17	3	0.0005-0.002	0
7	50	6	0.0001-0.0006	0
8	138	1	0.0002-0.0015	3
9	15.5	1	0.001	0
10	95	2	0.0003-0.0009	0
11	52	1	0.0005-0.0002	0
12	11	5	0.0004	0
13	47	2	0.0005-0.001	1