Vasopressin Improves Hemodynamic Status in Infants with Congenital Diaphragmatic Hernia

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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 fraction of inspired oxygen. In 6 of 13 patients, extracorporeal membrane oxygenation therapy was no longer indicated after treatment with vasopressin. Improvement in left ventricular function and oxygenation index after vasopressin initiation was associated with a decreased need for extracorporeal membrane oxygenation therapy. 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. *(J Pediatr 2014;165:53-8)*.

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.[1,2] In addition to respiratory insufficiency and persistent pulmonary hypertension of the newborn, 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 dysfunction secondary to suprasystemic pulmonary arterial pressure (PAP).[3-5] 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 often are 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] rate of ECMO use, 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 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

After 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

CDH	Congenital diaphragmatic hernia
ECMO	Extracorporeal membrane oxygenation therapy
FiO_2	Fraction of inspired oxygen
HR	Heart rate
LV	Left ventricular
MAP	Mean arterial pressure
NS	Not significant
OI	Oxygenation index
PAP	Pulmonary arterial pressure
SaO_2	Oxygen saturation

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was to assess the effect of vasopressin therapy on systemic and pulmonary hemodynamics and gas exchange and to document adverse effects. Data collected included demographics; severity of CDH; clinical course, including ventilator strategy and 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 before and after vasopressin therapy.

At our institution, the initial management of infants with CDH involves synchronized intermittent mandatory ventilation with volume guarantee (tidal volume 4-5 mL/kg). Peak pressures greater than 25-28 cm H_2O or the inability to ventilate (pCO_2 >65) with a respiratory rate greater than 50/min prompts the initiation of high-frequency oscillatory ventilation. Preductal arterial access (radial or brachial) is obtained in all patients and fraction of inspired oxygen (FiO_2) is titrated based on preductal pO2. Preductal arterial blood gasses more accurately reflect gas exchange in the lung with postductal arterial blood gasses representing a venoarterial admixture. Because of the high frequency of adrenal insufficiency in this population,[11] hydrocortisone (2 mg/kg) is administered to all patients on admission and daily random cortisol levels are used to determine the maintenance dose required (1-2 mg/kg every 8 hours).

For patients with persistent hypotension, dopamine (5-20 μg/kg/min) is initiated, followed by epinephrine (0.05-0.5 μg/kg/min). Hypotension is defined as a mean arterial pressure (MAP) less than gestational age or in the case of a narrow pulse pressure, systolic blood pressure ≤55 mmHg 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 decrease in systemic blood pressure results in right-to-left shunting through fetal conduits, leading to profound and life-threatening hypoxemia. In this setting, epinephrine often is initiated before reaching the maximum dose of 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 jet, right–to-left or bidirectional ductus arteriosus flow). Milrinone is initiated at 0.25 μg/kg/min for 6 hours then increased to 0.5 μg/kg/min and maintained at that dose with no further titration. Indications for ECMO include critical preductal hypoxemia (persistent preductal pO_2 <40 mmHg), refractory shock, and/or refractory acidosis.

Statistical analysis was conducted in Prism 6.0b (by GraphPad Software, Inc, La Jolla, California). Categorical variables were compared by use of the χ^2 test and continuous variables compared by use of a *t* test (normally distributed data) or Mann-Whitney 2-sample *U* test (nonparametric data). Comparisons between multiple groups were made with ANOVA. Statistical analysis was performed on the basis of 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 5 patients because of 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 high-frequency oscillatory ventilation. All patients received hydrocortisone and dopamine (range 15-25 μg/kg/min), and 11 of 13 (85%) received epinephrine (range 0.03-0.4 μg/kg/min) before the initiation of vasopressin. All patients met the criteria for ECMO cannulation.

In 11 of 13 patients, a trial of vasopressin infusion was initiated before ECMO therapy (range 0.0001-0.002 units/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**. After the administration of vasopressin, no patients required escalation of other vasopressor support, and epinephrine was weaned in 6 patients (median of 0.09 μg/kg/min, range 0.02-0.2 μg/kg/min), and dopamine was weaned in 4 patients (median of 6 μg/kg/min, range 5-15 μg/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 such 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 (n = 4) and refractory acidosis (n = 1).

At 12 hours after initiation of vasopressin, MAP increased from a mean of 47 ± 11.1 to 64 ± 8.8 (P = .0021), and heart rate (HR) decreased from a mean of 172 ± 18.2 to 133 ± 17.8 (P = .001) at 24 hours (**Figure 1**, A). **Figure 1**, B demonstrates similar changes in MAP and HR among those 6 patients who did not require ECMO therapy. Similarly, oxygen saturation (SaO_2) increased from 90.2% to 94.6% (P = not significant [NS]) and FiO_2 decreased from 79 ± 25.5% to 41 ± 16.9%