JPPT | Single Center Retrospective Study

Evaluation of Hyponatremia in Infants on Vasopressin Therapy

Caitlin Hawkins, PharmD; Brianna Hemmann, PharmD; and Trina Hemmelgarn, PharmD

OBJECTIVE Vasopressin has systemic vasoconstrictive yet pulmonary vasodilatory effects, making it an ideal agent for hypotension management in infants with congenital diaphragmatic hernia (CDH)–associated pulmonary hypertension. The side effects of vasopressin in this population, such as hyponatremia, are understudied. This study aims to characterize the effect of vasopressin on sodium concentrations in infants with and without CDH.

METHODS This was a retrospective review of patients who received vasopressin while admitted to a level IV neonatal intensive care unit. The primary outcome was the incidence of hyponatremia (blood sodium <135 mmol/L) during vasopressin therapy. Secondary outcomes included time to hyponatremia, dose and duration of vasopressin, incidence of severe hyponatremia (blood sodium <125 mmol/L), and hypertonic saline use. Both blood serum and blood gas sample sodium concentrations were used to compare CDH vs non-CDH patients.

RESULTS The average difference between baseline and lowest blood sodium was significant for both CDH and non-CDH patients for all samples ($p < 0.001$). There was no significant difference in the primary outcome, nor in the secondary outcomes of time to hyponatremia or duration of vasopressin infusion. The average dose of vasopressin was higher in the CDH vs non-CDH group ($p = 0.018$). The incidences of severe hyponatremia and hypertonic saline use were greater in the CDH vs non-CDH group for patients who had blood serum sodium samples collected ($p = 0.049$ and $p = 0.033$, respectively).

CONCLUSIONS This study showed that severe hyponatremia occurred more frequently in CDH vs non-CDH patients. Extreme caution is necessary when managing total body sodium in patients with CDH.

ABBREVIATIONS CDH, congenital diaphragmatic hernia; IV, intravenous; NICU, neonatal intensive care unit; TPN, total parenteral nutrition

KEYWORDS congenital diaphragmatic hernia; hyponatremia; neonatal intensive care unit; pulmonary hypertension; vasopressin

J Pediatr Pharmacol Ther 2024;29(4):385–390

DOI: 10.5863/1551-6776-29.4.385

Introduction

Vasopressin is an endogenous hormone secreted from the posterior pituitary that acts on various receptors in the vasculature and kidneys to influence hemodynamic stability and serum osmolarity.[1] It activates vasopressin 1a receptors in the vascular smooth muscle, causing vasoconstriction and subsequent increases to systemic vascular resistance and mean arterial pressure. It also activates vasopressin 2 receptors in the distal collecting duct of the kidney, inserting aquaporin channels and increasing water reabsorption.[1] Vasopressin is often used in cases of catecholamine-resistant shock or after cardiac surgery for cardiogenic shock. Based on recent literature, the use of vasopressin is on the rise in the neonatal intensive care unit (NICU) for hypotension and/or pulmonary hypertension.[1–3] Although vasopressin has systemic vasoconstrictive effects, it also has vasodilatory effects on pulmonary vasculature, which is thought to be mediated by endothelial nitric oxide release.[4]

Congenital diaphragmatic hernia (CDH) is a condition characterized by a diaphragm defect that allows abdominal organs and other contents to protrude into the thoracic cavity, affecting approximately 0.8 to 5 infants out of every 10,000 births.[5] The exact etiology is unclear, although it is often associated with multistructure and/or chromosomal anomalies. This condition is classified based on the location of the hernia: posterior lateral (Bochdalek) hernias are most common (>70%), followed by anterior (Morgagni) hernias (~25%) and central hernias (~5%).[5] Overall, CDH may lead to inadequate perfusion, lung hypoplasia, persistent pulmonary hypertension, and ventricular dysfunction of varying

severities.[5] The presence of heart defects, extensive lung hypoplasia, and liver herniation (protrusion into the thoracic cavity) are associated with increased life-sustaining needs, such as extracorporeal membrane oxygenation therapy, and decreased survival.[6] Infants with CDH consistently need treatment for pulmonary hypertension, and previous studies in patients with pulmonary hypertension have shown vasopressin to be beneficial in improving systemic hemodynamics while decreasing the risk of pulmonary vasculature damage.[7]

One of the common and concerning side effects associated with vasopressin therapy is hyponatremia. This is likely caused by V2 receptor activation, which has the potential to precipitate a dilutional hyponatremia by increasing water retention. Unrecognized or untreated severe acute hyponatremia can result in detrimental consequences due to the subsequent rapid brain swelling that can occur. Children are at a greater risk for these consequences because of the larger brain-to-intracranial volume ratio than adults, because there is less room to accommodate the swelling that occurs.[8] Infants, having skulls that are not fully fused, have the ability to accommodate cranial expansion, although the fontanelle does not appear to offer protection against hyponatremic encephalopathy.[9] Although hyponatremia has been observed with vasopressin administration in the postmarket period, there is conflicting evidence on the incidence of hyponatremia in the general population. In the CDH population specifically, there is a paucity of data because many studies excluded patients with congenital malformations or CDH.[1,2,4,8–13] This research project aims to provide a better understanding of the effect of vasopressin on blood sodium concentrations in NICU patients with and without CDH.

Materials and Methods

Patient Selection. This was a retrospective chart review of patients admitted to a level IV NICU who received a vasopressin intravenous (IV) infusion from January 1, 2016, to January 1, 2022. The inclusion criteria included any patient who received IV vasopressin while admitted to the NICU during the study period. Patients who received vasopressin for less than 6 hours, patients who were already on vasopressin when admitted to the NICU from an outside hospital or another unit, and patients with insufficient blood sodium data (one or fewer sodium values recorded) were excluded. Additionally, if a patient received multiple infusions of vasopressin therapy, they were considered part of the same course if the time between infusions was less than 48 hours.

Outcome Variables. The primary outcome was the incidence of any hyponatremia event (blood sodium concentration <135 mmol/L) stratified by CDH vs non-CDH patients. Secondary outcomes included time to hyponatremia after vasopressin initiation, dose and duration of vasopressin treatment, incidence of severe hyponatremia (blood sodium <125 mmol/L), and use of hypertonic saline. Secondary outcomes were only evaluated in patients who experienced a hyponatremia event. Additionally, average baseline blood sodium concentrations for all patients were compared to the lowest sodium observed during vasopressin therapy. The baseline blood sodium was defined as the average of up to 3 days of sodium concentrations prior to vasopressin initiation. Of note, both blood gas and blood serum sodium values were collected if available. Because there is no standardized comparison, values for serum and blood gas sodium concentrations were analyzed separately. If a patient had both blood gas and serum values recorded, they were analyzed in both groups. Additionally, if a patient had hyperglycemia (blood glucose >200 mg/dL) or used parenteral sodium supplementation during vasopressin infusion, it was noted during data collection. Parenteral sodium supplementation included total parenteral nutrition (TPN), or IV fluids that were administered for purposes other than to keep the line patent in patients not using TPN.

Statistical Analysis. Continuous variables, including blood sodium concentration, vasopressin dose, and duration of vasopressin, were reported as an average with SD and were compared using independent or paired *t* tests with a significance level of 0.05. Discrete variables (incidence of hyponatremia, incidence of severe hyponatremia, and use of hypertonic saline) were reported as a number and percentage of the sample and were compared using χ^2 tests with a significance level set to 0.05. Data analysis was performed using Minitab Workspace (version 1.3.1, Minitab).

Results

Of the 99 patients evaluated, 22 were excluded (11 because of vasopressin administration outside NICU, 9 for vasopressin administration less than 6 hours, 1 for vasopressin administration outside of study date range, and 1 for insufficient sodium data), and 12 patients had multiple vasopressin infusions; therefore, 89 total vasopressin courses in 77 unique patients were analyzed (Supplemental Figure). The baseline characteristics of gestational age at birth and birth weight were different between groups. Both were higher in the CDH group compared with the non-CDH group (36.9 ± 2.01 vs 33.2 ± 6.76 weeks, $p < 0.001$; and 2.8 ± 0.73 vs 2.1 ± 0.96 kg, $p < 0.001$, respectively; Table 1). The primary diagnosis at admission was CDH for 34 patients (38%) and non-CDH for 55 patients (62%). Further breakdown of primary diagnosis is shown in Table 2. There was no difference in incidence of hyperglycemia between groups, and no sodium values were adjusted prior to analysis.

For both the blood serum and blood gas sodium collection groups, the average baseline sodium was higher than the lowest sodium observed during vasopressin infusion for both CDH and non-CDH patients (Figure 1).

Table 1. Baseline Patient Characteristics

Variable	Total (n = 89)	CDH (n = 34)	Non-CDH (n = 55)	p value
Male sex, n (%)	51 (57)	18 (53)	33 (60)	0.513
Ethnicity, n (%)				0.800
White	58 (65)	24 (71)	34 (62)	
Black/African American	19 (21)	6 (18)	13 (24)	
Hispanic	2 (2)	1 (3)	1 (2)	
Other	10 (11)	3 (9)	7 (13)	
Gestational age at birth, mean ± SD, wk	34.6 ± 5.72	36.9 ± 2.01	33.2 ± 6.76	<0.001
Birth weight, mean ± SD, kg	2.4 ± 0.94	2.8 ± 0.73	2.1 ± 0.96	<0.001
Vasoactive agent use, n (%)*	80 (90)	34 (100)	46 (84)	0.013
1 agent	35 (39)	9 (26)	26 (47)	0.051
2 agents	35 (39)	18 (53)	17 (31)	0.039
3 agents	10 (11)	7 (21)	3 (5)	0.028
Stress corticosteroid use, n (%)†	78 (88)	30 (88)	48 (87)	0.893
Diuretic use, n (%)‡	27 (30%)	15 (44%)	12 (22%)	0.026
Furosemide	26 (96%)	14 (93%)	12 (100%)	0.051
Chlorothiazide	4 (15%)	2 (13%)	2 (17%)	0.619
Bumetanide	7 (26%)	5 (33%)	2 (17%)	0.059
Supplemental sodium use, n (%)	87 (98%)	32 (94%)	55 (100%)	0.069
TPN	75 (84%)	29 (85%)	46 (84%)	0.835
IV fluid§	12 (13%)	3 (9%)	9 (16%)	0.040
ECMO, n (%)	12 (13%)	11 (32%)	1 (2%)	< 0.001
Survival to discharge	33 (37%)	8 (24%)	25 (45%)	0.037

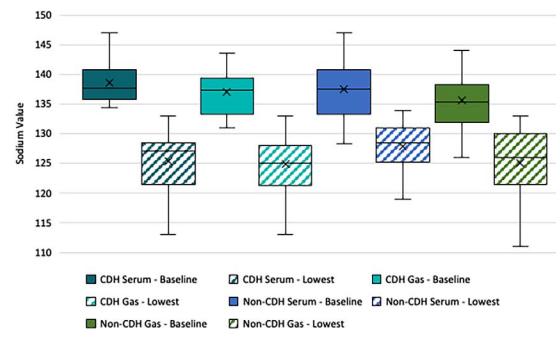
ECMO, extracorporeal membrane oxygenation; IV, intravenous; TPN, total parenteral nutrition

* Vasoactive agents include epinephrine, norepinephrine, phenylephrine, dopamine, and dobutamine.
† Stress corticosteroid use was defined as any patient on hydrocortisone ≥2 mg/kg/day.
‡ Patients could be on any combination of diuretics.
§ An IV fluid is defined here as any administration of sodium in an IV fluid that was administered above the rate to keep the vein open (1 ml/min), even if that was a singular bolus.

Table 2. Primary Diagnosis Upon Neonatal Intensive Care Unit Admission

Condition	Number
Pulmonary hypertension	3
Necrotizing enterocolitis	3
Patent ductus arteriosus	3
Bladder outlet obstruction	10
Multicystic dysplastic kidney	12
Congenital diaphragmatic hernia	34
Other	24

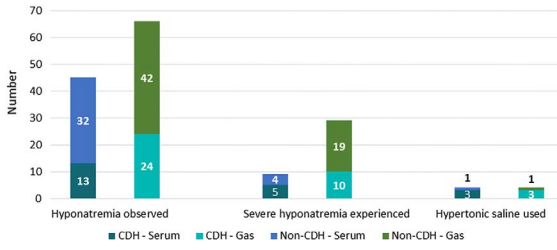
Figure 1. Baseline and lowest sodium concentration in all patient groups.



CDH, congenital diaphragmatic hernia.

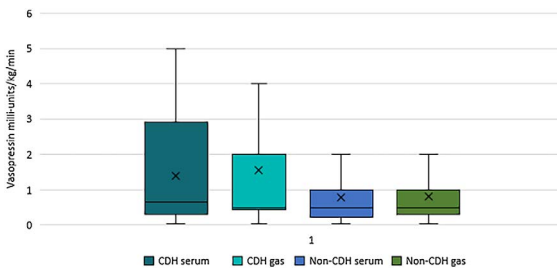
Although there was an evident decrease in sodium, there was not a significant difference in the incidence of hyponatremia. For the serum collection group (n = 72), 13 of 26 CDH patients (50%) and 32 of 46 non-CDH patients (70%) experienced hyponatremia (p = 0.100), whereas in the blood gas collection group (n = 87), the primary end point was experienced by 24 of 33 CDH patients (73%) and 42 and 54 non-CDH patients (78%; p = 0.593; Figure 2).

Figure 2. Incidence of hyponatremia, severe hyponatremia, or hypertonic saline use.



CDH, congenital diaphragmatic hernia.

Figure 3. Dose of vasopressin.



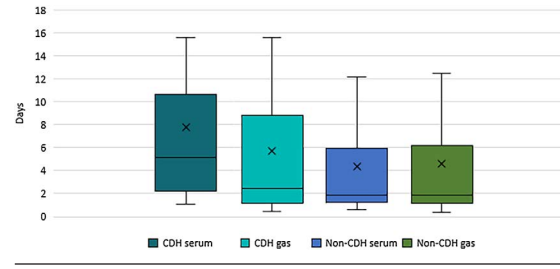
CDH, congenital diaphragmatic hernia.

For those who experienced hyponatremia, the average dose of vasopressin required was greater for CDH vs non-CDH patients for the blood gas sodium collection group only (1.55 ± 1.99 vs 0.82 ± 0.77 milli-units/kg/min; p = 0.018; Figure 3). There was no difference found in the duration of vasopressin use (Figure 4) or in the time to hyponatremia between groups (Figure 5). Most noticeably, as outlined in Figure 2, the serum collection group had 5 CDH patients (38%) and 4 non-CDH patients (13%) who experienced severe hyponatremia (p = 0.049). For the blood gas collection group, there was not a statistically significant difference (10 [42%] vs 19 [45%]; p = 0.779). This also correlated to the number of patients who received hypertonic saline; however, only 4 patients met this secondary objective (Figure 2).

Discussion

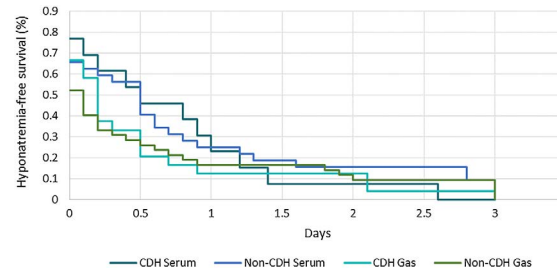
In this single-center, retrospective study, we found that severe hyponatremia is more likely to occur in CDH vs non-CDH patients (Figure 2). The decline in blood sodium concentration across all study populations after vasopressin initiation was stark, because there was a significant difference between the average baseline and lowest blood sodium values in all study groups (Figure 1). Some values spanned the 110 to 115 mmol/L range, putting these patients at a significant risk for seizures, coma, and death.[8] Of note, although some form of parenteral sodium supplementation was given

Figure 4. Duration of vasopressin use.



CDH, congenital diaphragmatic hernia.

Figure 5. Time to hyponatremia.



alongside vasopressin infusion for 87 of 89 courses (98%), significant hyponatremia still occurred (Table 1). For most patients, this decrease in blood sodium occurred within the first 12 to 24 hours after vasopressin initiation, which is consistent with what has been seen in previous studies[1,7,9,11] (Figure 5). Although a transient decrease in blood sodium after vasopressin initiation has been noted in multiple studies,[1,8–11] the duration of vasopressin exposure may play a role in the incidence of hyponatremia as well, as observed by both Acker et al[7] and Davalos et al.[8] This study found that although the average duration (days) of vasopressin was higher in the CDH population for those that experienced hyponatremia, there was no statistically significant difference in treatment duration between CDH and non-CDH populations for both serum (7.76 ± 8.21 vs 4.31 ± 4.91, p = 0.177) and blood gas (5.67 ± 6.81 vs 4.60 ± 5.11, p = 0.510) collection groups (Figure 4). Additionally, patients with CDH had increased acuity compared with non-CDH patients, such as use of multiple vasoactive agents, diuretics, extracorporeal membrane oxygenation, and increased vasopressin dose requirements (Table 1). The life-sustaining measures needed for this greater acuity could have contributed as well to the risk of hyponatremia. For example, the CDH group had more patients using at least 1 diuretic, which could have perpetuated an increased sodium loss. Additionally, the average dose of vasopressin (milli-units/kg/min) used was greater in the CDH group both overall (1.48 ± 1.81 vs 0.85 ± 0.78, p = 0.008) and among those experiencing hyponatremia (blood gas collection group, 1.55 ± 1.99

vs 0.82 ± 0.77; p = 0.018; Figure 3). These doses were higher than those often reported in neonatal studies (0.2–0.7 milli-units/kg/min),[2] a finding similar to the cases reported by Leister and colleagues,[11] who noted that their patients with congenital heart diseases required higher than usual doses of vasopressin and experienced severe hyponatremia. As seen in both previous studies as well as this study, the incidence of severe hyponatremia may be vasopressin dose dependent. Additionally, the survival to discharge was significantly greater in the non-CDH population. It is interesting to note, however, that the gestational age and birth weight were greater in the CDH group, especially as previous literature notes that a shorter gestational age is independently associated with a greater hyponatremia risk[13] (Table 1). Overall, although these patients with CDH were further developed, hyponatremia still occurred more frequently.

To evaluate sodium dynamics, both blood serum and blood gas concentrations were used if available. Serum sodium concentrations are obtained from plasma, whereas blood gas concentrations are obtained from whole blood, and therefore require less blood to be removed. There is a slight variation in the reported sodium between these techniques because of the differences in analyzers. There is no standardized comparison between the two, although both are used to drive clinical decision-making.

Given the incidence of severe hyponatremia noted in this study and the risks associated with this condition, further investigation is needed to evaluate how to maintain adequate blood sodium concentrations. Because vasopressin can potentiate a dilutional hyponatremia, free water restriction and sodium supplementation could be beneficial, as was similarly noted in previous studies.[3,7,8] Additionally, hypertonic saline was used in 4 patients in this study and remains an option for replacement; however, extreme caution is warranted in this patient population.

Although there are previous studies and case reports that include CDH patients that note hyponatremia is a risk with vasopressin use, this study was unique in how it specifically compared the incidence of hyponatremia in CDH vs non-CDH patients. Overall, 89 vasopressin courses were evaluated in 77 unique patients, which, given the incidence of CDH in the general population, means this study was able to capture a large sample of patients with this condition.

A limitation of this study is the absence of a standardized comparison between blood gas and serum sodium concentrations, which hampered how the data could be pooled for analysis. Additionally, because this was a retrospective chart review, the timing of serum or blood gas collection related to vasopressin infusion initiation or discontinuation was not consistent between patients. Finally, although it was documented if each patient was receiving sodium supplementation from IV fluids or TPN at the time of vasopressin use, the specific amount of sodium received was not recorded. Further studies are needed to more accurately describe the patients' full sodium concentration sequence.

Conclusion

Although hyponatremia is a known adverse effect of vasopressin, characterizing the severity of this hyponatremia can help health care providers make informed decisions about sodium management. The findings of this study indicate that extreme caution is necessary when managing NICU patients receiving vasopressin, especially in the CDH patient population, given the significant decrease in sodium concentration in both serum and blood gas determinations. Further studies are warranted to evaluate adequate sodium repletion in patients using vasopressin, and overall, increased vigilance is necessary to ensure the patient's sodium requirement is met.

Article Information

Affiliations. Department of Pharmacy (CH*), Nationwide Children's Hospital, Columbus, OH; Division of Pharmacy (BH, TH), Cincinnati Children's Hospital Medical Center, Cincinnati, OH. *CH was a student at the time of this study

Correspondence. Caitlin Hawkins, PharmD; caitlin.hawkins@nationwidechildrens.org

Disclosures. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, informed consent was not required, and the appropriate committees at our institution (Cincinnati Children's Hospital, 2002-0261; May 2, 2022) approved a waiver of the requirement to obtain a signed Authorization to Use and Disclose Protected Health Information for Research.

Acknowledgments. Results were presented at the Pediatric Pharmacy Association Fall Conference in Columbus, OH, on September 24, 2022; and at the American Society of Health-System Pharmacists Midyear Clinical Meeting in Las Vegas, NV, on December 6, 2022.

Submitted. October 6, 2023

Accepted. January 7, 2024

Supplemental Material. DOI: 10.5863/1551-6776-29.4.385.S1

References

1. Budniok T, Elsayed Y, Louis D. Effect of vasopressin on systemic and pulmonary hemodynamics in neonates. *Am J Perinatol*. 2021;38(12):1330–1334.

2. Ni M, Kaiser JR, Moffett BS, et al. Use of vasopressin in neonatal intensive care unit patients with hypotension. *J Pediatr Pharmacol Ther.* 2017;22(6):430–435.
3. Shah S, Dhalait S, Fursule A, et al. Use of vasopressin as rescue therapy in refractory hypoxia and refractory systemic hypotension in term neonates with severe persistent pulmonary hypertension-a prospective observational study [published online ahead of print December 21, 2022]. *Am J Perinatol*. 10.1055/a-1969-1119
4. Malikiwi A, Ferguson P, Sehgal A. Vasopressin in perioperative management of congenital diaphragmatic hernia: a case report. *Ann Pediatr Surg*. 2017;13:47–49.
5. Chandrasekharan PK, Rawat M, Madappa R, et al. Congenital diaphragmatic hernia–a review. *Matern Health Neonatol Perinatol*. 2017;3:6.
6. Chatterjee D, Ing R, Gien, J. Update on congenital diaphragmatic hernia. *Anesth Analg*. 2020;131(3):808–821.
7. Acker SN, Kinsella JP, Abman SH, Gien J. Vasopressin improves hemodynamic status in infants with congenital diaphragmatic hernia. *J Pediatr*. 2014;165(1):53–58.
8. Davalos MC, Barrett R, Seshadri S, et al. Hyponatremia during arginine vasopressin therapy in children following cardiac surgery. *Pediatr Crit Care Med*. 2013;14(3):290–297.
9. Moritz ML, Ayus JC. New aspects in the pathogenesis, prevention, and treatment of hyponatremic encephalopathy in children. *Pediatr Nephrol*. 2010;25(7):1225–1238.
10. Mohamed AA, Louis D, Surak A, et al. Vasopressin for refractory persistent pulmonary hypertension of the newborn in preterm neonates–a case series. *J Matern Fetal Neonatal Med*. 2022;35(8):1475–1483.
11. Leister N, Rohe D, Schumacher C, et al. Severe hyponatraemia associated with the use of arginine-vasopressin in two neonates with complex congenital heart disease. *J Pediatr Intensive Care*. 2020;9(3):213–215.
12. Bigelow AM, Ghanayem NS, Thompson NE, et al. Safety and efficacy of vasopressin after Fontan completion: a randomized pilot study. *Ann Thorac Surg*. 2019;108(6):1865–1874.
13. Kiem Hao T. Prevalence and risk factors for hyponatremia in preterm infants. *Open Access Maced J Med Sci*. 2019;7(19):3201–3204.