Saudi Pharmaceutical Journal 30 (2022) 1107–1112

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Vasopressin associated hyponatremia in critically ill children: A cross-sectional study

Yousif S. Alakeel [a,b,c,*], Meshary M. Alkahtani [a,b,c], Omar M. Hijazi [b,d,e], Mohammad M. Algahtani [f]

[a] College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[b] King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
[c] Department Pharmaceutical Care Services, King Abdulaziz Medical City, Ministry of the National Guard-Health Affairs, Riyadh, Saudi Arabia
[d] College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
[e] Division of Pediatric Cardiology, Cardiac Sciences, King Abdulaziz Medical City, Ministry of the National Guard - Health Affairs, Riyadh, Saudi Arabia
[f] Department of Pharmacology and Toxicology, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 5 March 2022
Accepted 10 June 2022
Available online 13 June 2022

Keywords:
Vasopressin
Hyponatremia
Pediatrics
Antidiuretic hormone
Pediatric cardiology
Shock

ABSTRACT

Background: The association of hyponatremia with vasopressin therapy in children is controversial. We aimed to evaluate the incidence and severity of hyponatremia associated with the administration of vasopressin in critically ill pediatric patients.
Methods: This retrospective cross-sectional study included children younger than 14 years who were admitted to the pediatric or pediatric cardiac intensive care units and received vasopressin for at least 24 h.
Results: In total, 176 critically ill pediatric patients were enrolled, with a median age of 22 days (7.3–146). The mean sodium level was notably decreased from 143.5 mEq/L ± 7.15 at the baseline to 134.3 mEq/L ± 7.7 at the 72-hour measurement after the initiation of vasopressin and varied significantly at all intervals from the baseline measurement ($P < 0.001$). Twenty-four hours after the discontinuation of vasopressin, more than half of the patients had hyponatremia. The highest proportion had mild hyponatremia (32.8%), followed by moderate hyponatremia (13.1%), and profound hyponatremia (7.5%). The incidence of hyponatremia was independent of gender (P = 0.94) or age group (P = 0.087). However, more than two-thirds of the moderate-profound cases and more than one-third of mild cases were observed in the neonate group (P = 0.043). The vasopressin dose did not affect the incidence ($P = 0.25$) or the severity of the hyponatremia ($P = 0.56$). Notably, all laboratory and hemodynamic parameters varied significantly at the end of therapy, compared to the baseline.
Conclusions: Continuous monitoring for hyponatremia when children are placed on vasopressin is essential to protect against more severe complications.

1. Introduction

Vasopressin is an antidiuretic hormone analog, frequently used to improve blood pressure in hemodynamically unstable children (Lechner et al., 2007; Mastropietro et al., 2008; Jerath et al., 2008; Mastropietro et al., 2010; Alten et al., 2012; Demiselle et al., 2020). Current guidelines recommend vasopressin as second line treatment if norepinephrine failed to maintain the mean blood pressure (MAP) goal or as an adjuvant therapy to decrease the dosing requirement of norepinephrine in patients with vasoplegic shock (Rhodes et al., 2017). Vasopressin improves the blood pressure through the activation of the V1 receptors, which results in an increased systemic vascular resistance and mean arterial blood pressure (Japundžić-Žigon et al., 2020). With lower doses, it stimulates the V2 receptors causing an antidiuretic effect (Product Information, 2014). Vasopressin has a procoagulant property that is mediated by the stimulation of the V1a receptors, leading to platelet aggregation, and the V2 receptors leading to the release of coagulation factors (Demiselle et al., 2020). It is noteworthy that vasopressin administration may induce hyponatremia through a

* Corresponding author at: College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Saudi Arabia.
E-mail address: alaqeely@ksau-hs.edu.sa (Y.S. Alakeel).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2022.06.006
1319-0164/

non-defined mechanism of action. A possible explanation of this phenomenon is through free water retention precipitated by the stimulation of the V2 receptors in the kidneys (Davalos et al., 2013). It is worth mentioning that hospital-acquired hyponatremia occurs in 17% to 45% of hospitalized children (Choong et al., 2011). Critically ill children with certain comorbidities, such as a congenital heart defect, are at an increased risk for neurodevelopmental abnormality, mandating the close monitoring of hyponatremia during hospitalization (Massaro et al., 2008; Donofrio and Massaro, 2010).

Limited literature describes the occurrence of hyponatremia after the administration of vasopressin therapy in pediatric patients post-cardiac surgery. Davalos et al. reported that the incidence of hyponatremia in pediatric patients, who received a vasopressin infusion, for hemodynamic instability following complex cardiac surgery, occurred in nearly half of the patients (Davalos et al., 2013). Another study reported lower serum sodium concentrations in the first 48 h in neonates with complex heart disease who received vasopressin, compared to the group without the medication (Alten et al., 2012). Some studies that evaluated the use of vasopressin in adult and pediatric patients with vasodilatory shock did not report any increase in the incidence of hyponatremia associated with the vasopressin therapy (Obritsch et al., 2004; Russell et al, 2008; Choong et al., 2009). The incidence of hyponatremia has been described in many studies where vasopressin was used in non-cardiac patients. A randomized trial, examining the use of low-dose vasopressin (0.005 units/kg/min) in non-septic critically ill children, observed that the low-dose vasopressin infusion was associated with a high incidence of hyponatremia (Baldasso et al., 2009). In addition, a higher rate of hyponatremia was observed following the administration of a high vasopressin dose (0.4 units/min) for the treatment of patients with acute variceal hemorrhage (Kravetz et al., 1984).

Overall, the association of hyponatremia with vasopressin therapy in children is controversial. The current study aimed to evaluate and describe the incidence and severity of hyponatremia associated with the administration of vasopressin infusion in critically ill pediatric patients.

2. Methods

2.1. Design and settings

This was a retrospective cross-sectional study, approved by King Abdullah International Medical Research Center (KAIMRC), to evaluate the incidence and severity of hyponatremia associated with the administration of vasopressin in pediatric patients in intensive care units (ICU). The study was conducted at King Abdulaziz Medical City, Riyadh (KAMC-R) and it included patients admitted to the pediatric intensive care units (PICU) or pediatric cardiac intensive care unit (PCICU). Vasopressin was used in doses ranging from 0.0003 to 0.001 units/kg/hour to maintain the mean blood pressure for hemodynamically unstable children.

2.2. Participants

All children who received vasopressin therapy from December 2016 to December 2020, at the PICU or PCICU were screened for eligibility. Children younger than 14 years who received vasopressin for at least 24 h were included in the analysis. Patients who received vasopressin for <24 h were excluded.

2.3. Outcome measures

The hospital's health electronic system was the primary source for data collection. Baseline characteristics for all the eligible patients were collected, including age, weight, height, gender, patient type (surgical cardiac, non-surgical cardiac medical, or non-cardiac patient), cardiopulmonary bypass (CPB) exposure, ICU length of stay (LOS), and concomitant medications. In addition, the laboratory results including serum lactate, renal function tests (serum creatinine, BUN), platelet count, INR, liver function tests (Bilirubin, AST, ALT), and relevant hemodynamic parameters (i.e., mean arterial pressure (MAP), BP, HR) and urine output (UO), were documented at baseline and after vasopressin initiation. The sodium levels were also recorded at baseline, and every 12 h for three days. The vasopressin therapy variables included the initial dose, dosage changes, and duration of therapy. The type of fluid therapy for hyponatremia, if available, was also documented.

The primary outcome of the study was the incidence and severity of hyponatremia associated with vasopressin and the change in the serum sodium levels from baseline and 12-hour intervals (12hrs, 24hrs, 36hrs, 48hrs, 60hrs, and 72hrs) and 24 h after discontinuation of the vasopressin infusion. Hyponatremia was classified based on the European and American definitions of hyponatremia as mild (135 to 130 mEq/L), moderate (129 to 125 mEq/L), or profound (<125 mEq/L) (Spasovski et al., 2014; Verbalis et al., 2013). The secondary outcomes included the association of the incidence or the severity of the hyponatremia with the vasopressin dose, and the effect of vasopressin use on other laboratory parameters and the severity of the vasopressin-associated hyponatremia that necessitated treatment.

2.4. Sample size calculation

According to a study conducted by Davalos et al., hyponatremia occurred in nearly 48% of children recovering from cardiothoracic surgery after the initiation of arginine vasopressin therapy (Davalos et al., 2013). During the past four years, 267 children received vasopressin based on the hospital's records. Using OpenEpi, the minimum required sample size was 174 with a 5% significance level and a 10% correction factor.

2.5. Statistical analysis

The data were analyzed with SPSS version 25.0. The qualitative data are presented as frequency and percentage, and the quantitative data as mean ± SD or as median (IQR). A Chi-square test or Fisher's exact test were used to determine the correlation between the nominal variables, and the Mann-Whitney's test for the relationship between the nominal and ordinal variables. A Wilcoxon test was used to track the change of a quantitative variable over different measurements. The Spearman test was used to analyze the change of the severity of hyponatremia with dose changes, and an Independent-*t*-test to describe the effect of the latter on the incidence of hyponatremia.

3. Results

3.1. Sample characteristics

The baseline characteristics of the sample are presented in Table 1. In total, 176 pediatric patients were enrolled with a median age of 22 days (7.3–146). The majority was neonates (54.3%, n = 95), followed by infants (30.9%, n = 54) and male (60.2%,

Table 1
Baseline Data (N = 176); N (%) unless otherwise stated.

Demographic	Category	Frequency (%)
Age (days)	Median (IQR)	22 (7.3–146)
Age category	Neonates < 1 month	95 (54.3)
	Infants (1–12 months)	55 (31)
	Young Child (1 – 6 years)	19 (10.9)
	Old child (7–14 years)	7 (4)
Gender	Female	70 (39.8)
	Male	106 (60.2)
Weight (kg)	Median (IQR)	3 (2.5–5.4)
Height (cm)	Mean ± SD	55.8 ± 22.96
	Median (IQR)	50 (46–60)
Type of patient	Surgical cardiac	117 (66.5)
	Non-surgical cardiac "medical"	15 (8.5)
	Non cardiac patient	44 (25)
Cardiopulmonary bypass (CPB)	Non-exposed	62 (35.2)
	Exposed	114 (64.8)
Baseline Clinical data		
Concomitant medications	Furosemide IV intermittent	29 (16.5)
	Furosemide continuous infusion	103 (58.5)
	Bumetanide	2 (1.1)
	Milrinone	100 (56.8)
	Norepinephrine	31 (17.6)
	Epinephrine	130 (73.9)
	Dopamine	36 (20.5)
	Nitroprusside	23 (13.1)
	Beta blocker	2 (1.1)
	Steroids	39 (22.2)
	ACEI	1 (0.6)
ICU Length of stay (LOS) (days)	Mean ± SD	38.9 ± 32.5
	Median (IQR)	30 (17–49.25)

n = 106). Most of the sample (66.5%, n = 117), had cardiac surgery. Of the cardiac surgery group, 114 (64.8%) received cardiopulmonary bypass (CPB) surgery. Concomitant with the vasopressin therapy, the majority (73.9%, n = 130), received epinephrine, furosemide continuous infusion (58.5%, n = 103), or milrinone (56.8%, n = 100). Dopamine, norepinephrine, and nitroprusside were received by 36 (20.5%), 31 (17.6%), and 23 (13.1%) patients respectively.

3.2. Primary outcomes

The change in the serum sodium levels from baseline, the 12-hour intervals and after the discontinuation of the infusion is presented in Table 2. Over the 72 h following vasopressin initiation, the mean sodium level decreased from 143.5 mEq/L ± 7.15 at baseline to 134.3 mEq/L ± 7.7 at the 72-hours measurement and varied at all the intervals from the baseline ($P < 0.001$). The sodium level increased slightly 24 h after the discontinuation of the infusion; however, it was significantly different from the baseline level ($P < 0.001$).

Table 2
The change in serum sodium levels from baseline at 12-hour intervals and after discontinuation of the infusion.

Sodium level (mEq/L): Mean ± SD			p-value
Baseline (n = 176)		143.5 ± 7.15	Reference
After initiation of the infusion	12hrs (n = 163)	142.09 ± 7.8	<0.001[a]
	24hrs (n = 140)	140.5 ± 7.5	<0.001[a]
	36hrs (n = 130)	137.76 ± 7.4	<0.001[a]
	48hrs (n = 77)	135.9 ± 8.4	<0.001[a]
	60hrs (n = 77)	135.16 ± 7.6	<0.001[a]
	72hrs (n = 48)	134.3 ± 7.7	<0.001[a]
24 h after discontinuation of the infusion (n = 174)		135.23 ± 7.3	<0.001[a]

[a] : Wilcoxon's test.

The incidence and severity of hyponatremia are reported in Table 3. The incidence of hyponatremia increased from 32 (22.9%) 24 h after the infusion initiation to 38 (49.4%) after 48 h. The mild hyponatremia cases increased from 22 (15.7%) to 25 (32.5%), moderate hyponatremia from 5 (3.6%) to 6 (7.8%), and profound hyponatremia was observed in 7 (9.1%) patients 48 h after vasopressin initiation, compared to 5 (3.6%) after 24 h of receiving the infusion. Twenty-four hours after discontinuing the vasopressin, more than half of the patients still had hyponatremia. The majority of this group had mild hyponatremia 57 (32.8%), followed by moderate hyponatremia 23 (13.1%), and profound hyponatremia, 13 (7.5%).

3.3. Secondary outcomes

The relationship between the incidence or severity of the hyponatremia and the demographic and clinical variables is documented in Table 4. No significant association was observed between the vasopressin dose and the incidence of hyponatremia ($P = 0.25$) or the severity ($P = 0.56$). The incidence of hyponatremia was also independent of gender ($P = 0.94$) or age group ($P = 0.087$). However, more than two-thirds of the moderate-profound cases and more than one-third of the mild cases were observed in the neonates ($P = 0.043$). Most of the cases observed in the neonates were mild (P = 0.022), but the severity of the hyponatremia did not differ in the other age groups. The surgical-cardiac patients experienced more hyponatremia, (60%, n = 57) ($P = 0.049$), compared with 30 (31.6%) in the non-cardiac patients ($P = 0.029$). Notably, the majority (69.2%, n = 9) of the profound hyponatremia cases were non-cardiac, with the mild cases occurring mainly in the surgical cardiac patients (73.7%, n = 42). More than half of the hyponatremic group (57.9%, n = 55) had CPB surgery ($P = 0.039$). Most of the moderate-profound cases occurred in patients who did not receive CPB, with three-quarters of the mild cases occurring in the CPB group ($P < 0.001$).

Table 5 displays the impact of the vasopressin dose on the laboratory and hemodynamic parameters. Notably, all the laboratory and hemodynamic parameters varied significantly at the end of therapy, compared to the baseline measurements. The INR, platelet count, and heart rate were decreased ($P < 0.001$); however, the serum lactate, MAP, as well as the liver and kidney function tests were significantly increased.

Lastly, the need for hyponatremia treatment or the type of fluid used did not differ based on the severity of the hyponatremia

Table 3
The Incidence/severity of hyponatremia associated with vasopressin: Frequency (%).

Hyponatremia	After vasopressin initiation		24 h post-treatment (n = 174)
	24 h (n = 140)	48 h (n = 77)	
Normal sodium level	108 (77.1)	39 (50.6)	81 (46.6)
Mild – from 135 to 130 mEq/L	22 (15.7)	25 (32.5)	57 (32.8)
Moderate – from 129 to 125 mEq/L	5 (3.6)	6 (7.8)	23 (13.1)
Profound – <125 mEq/L	5 (3.6)	7 (9.1)	13 (7.5)

Table 4
The association between the incidence or severity of hyponatremia and the patients' demographic and clinical variables; N(%) unless otherwise stated.

		Hypo-natremia (n = 95)	p-value	Mild hyponatremia (n = 57)	Moderate hyponatremia (n = 23)	Profound hyponatremia (n = 13)	p-value
Vasopressin dose (units/Kg/hour)	mean ± SD	0.0006 ± 0.0004	0.25 [a]	0.0007 ± 0.0003	0.0005 ± 0.0005	0.0006 ± 0.0005	0.56
Gender	Males (n = 106)	57 (60)	0.94	33 (57.9)	17 (73.9)	6 (46.2)	0.39
	Females (n = 70)	38 (40)		24 (42.1)	6 (26)	7 (53.8)	
Age groups	Neonates (n = 94)	48 (50.5)	0.27	22 (38.6)	16 (69.6)	9 (69.2)	0.022
	Infants (n = 55)	34 (35.8)	0.12	25 (43.9)	6 (26)	3 (23.1)	0.413[c]
	Young Child (n = 18)	9 (9.5)	0.52	8 (14)	0	0	0.12[c]
	Old child (n = 7)	4 (4.2)	0.59[b]	2 (3.5)	1 (4.3)	1 (7.7)	0.7[c]
Type of patient n (%)	Surgical cardiac (n = 115)	57 (60)	0.049	42 (73.7)	9 (39)	4 (30.8)	0.001[c]
	non-surgical cardiac "medical" (n = 15)	8 (8.4)	0.95	5 (8.7)	3 (13)	0	0.88[c]
	Non- cardiac patient (n = 44)	30 (31.6)	0.029	10 (17.5)	11 (47.8)	9 (69.2)	0.68[c]
Cardiopulmonary bypass (CPB) exposure	Non exposed (n = 62)	40 (42.1)	0.039	14 (24.6)	15 (65.2)	11 (84.6)	<0.001
	Exposed (n = 114)	55 (57.9)		43 (75.4)	8 (34.8)	2 (15.4)	

[a] Independent student-t-test.
[b] Fisher's exact test.
[c] Mann Whitney's test.

Table 5
The association between the incidence or severity of hyponatremia and the patients' demographic and clinical variables; N(%) unless otherwise stated.

		Hypo-natremia (n = 95)	p-value	Mild hyponatremia (n = 57)	Moderate hyponatremia (n = 23)	Profound hyponatremia (n = 13)	p-value
Vasopressin dose (units/Kg/hour)	mean ± SD	0.0006 ± 0.0004	0.25 [a]	0.0007 ± 0.0003	0.0005 ± 0.0005	0.0006 ± 0.0005	0.56
Gender	Males (n = 106)	57 (60)	0.94	33 (57.9)	17 (73.9)	6 (46.2)	0.39
	Females (n = 70)	38 (40)		24 (42.1)	6 (26)	7 (53.8)	
Age groups	Neonates (n = 94)	48 (50.5)	0.27	22 (38.6)	16 (69.6)	9 (69.2)	0.022
	Infants (n = 55)	34 (35.8)	0.12	25 (43.9)	6 (26)	3 (23.1)	0.413[c]
	Young Child (n = 18)	9 (9.5)	0.52	8 (14)	0	0	0.12[c]
	Old child (n = 7)	4 (4.2)	0.59[b]	2 (3.5)	1 (4.3)	1 (7.7)	0.7[c]
Type of patient n (%)	Surgical cardiac (n = 115)	57 (60)	0.049	42 (73.7)	9 (39)	4 (30.8)	0.001[c]
	non-surgical cardiac "medical" (n = 15)	8 (8.4)	0.95	5 (8.7)	3 (13)	0	0.88[c]
	non– cardiac patient (n = 44)	30 (31.6)	0.029	10 (17.5)	11 (47.8)	9 (69.2)	0.68[c]
Cardiopulmonary bypass (CPB) exposure	Non exposed (n = 62)	40 (42.1)	0.039	14 (24.6)	15 (65.2)	11 (84.6)	<0.001
	Exposed (n = 114)	55 (57.9)		43 (75.4)	8 (34.8)	2 (15.4)	

[a] Independent student-t-test.
[b] Fisher's exact test.
[c] Mann Whitney's test.

Table 6
Characteristics of vasopressin-associated hyponatremia that necessitated treatment (n = 161).

Fluid therapy	Mild (n = 57)	Moderate/profound (n = 104)	p-value
Required treatment (n = 143)	48 (84.2)	95 (91.3)	0.169
Type of fluid			
0.9% NACL (n = 61)	20 (35.1)	41 (39.4)	0.58[a]
0.45% NACL (n = 81)	28 (49.1)	53 (50.9)	0.82 [a]
0.225% NACL (n = 1)	0	1 (0.96)	0.64 [a]
3% NACL or Albumin 5% or Albumin 20%	0	0	NA

[a] :Mann Whitney's test.

(P = 0.169) (Table 6). The 0.45% and 0.9% NaCl were most frequently used, and the 3% NaCl and albumin solutions were not used.

4. Discussion

Hyponatremia, defined as a decreased serum sodium level below 135 mEq/L, is the most frequently occurring electrolyte imbalance in clinical practice (Bockenhauer and Zieg, 2014). Hyponatremia mostly occurs due to increased water retention due to an abnormal or normal antidiuretic hormone (ADH) secretion, rather than sodium wasting (Bockenhauer and Zieg, 2014). In this study, a decline in the sodium levels occurred directly following the administration of vasopressin in the pediatric patients treated for a cardiac or non-cardiac indication, similar to literature (Alten et al., 2012; Davalos et al., 2013; Baldasso et al. 2009; Kra-

vetz et a. 1984). Several factors in this study increased the incidence and severity of the hyponatremia. The baseline mean sodium level was normal (143.5 mEq/L ± 7.15); however, after the vasopressin initiation, the mean sodium level decreased, and approximately half of the patients developed hyponatremia (49.4%) after 48 h and more than half (53.4%) continued to have hyponatremia 24 h after the treatment discontinuation. Similarly, hyponatremia was observed in half of the pediatric patients who received vasopressin infusion due to hemodynamic instability post complex cardiac surgery, as reported by Davalos et al. (Davalos et al., 2013). Alten et al., 2012, reported that, compared to patients without vasopressin, lower sodium levels were observed in the neonates with complex heart disease. However, using vasopressin for vasodilatory shock in adult and pediatric patients did not result in increased hyponatremia (Obritsch et al., 2004; Choong et al., 2009).

Currently available clinical data recommend the use of vasopressin as rescue therapy in critically ill children in cases of refractory shock and cardiac arrest (24). In a review of 51 reports related to vasopressin by Argawal et al., vasopressin was mostly used for the different forms of catecholamine-resistant shock, including septic, post-cardiotomy, other vasodilatory/mixed shock, and cardiac arrest (Agrawal et al., 2012). The patients enrolled in this study were primarily surgical-cardiac patients, (66.5%, n = 117), or prior exposure to CPB surgery (64.8%), and most were neonates (54.3%, n = 95). This highlights the fact that neonatal kidneys have a decreased glomerular filtration rate with immature distal nephrons, compared with other age groups, increasing their susceptibility to hemodynamic instability requiring the use of vasopressin (Bizzarri et al., 2016), and a greater variability of the electrolytes from baseline. This supports the finding that more than two-thirds of the moderate-profound cases occurred in the neonate group ($P = 0.043$).

With the vasopressin, the majority of the sample was also receiving the vasoactive agent with inotropic properties, epinephrine (73.9%) or the inotrope milrinone (56.8%). These agents are preferred by the current pediatric guidelines in cases of cold shock that usually predominate in children, in contrast, warm shock necessitate the use of vasopressor agents (e.g., norepinephrine) that increase the Systemic Vascular Resistance (SVR). Vasopressin is recommended when either of these agents fail or as a supplementary agent to decrease the dosing requirements. However, in the Choong et al. randomized clinical trial, the use of low-dose vasopressin in pediatric vasodilatory shock, as an adjunctive agent to vasoactive agents did not provide any added benefit (Choong et al., 2009). In our study, however, the mean heart rate was significantly decreased ($P < 0.001$), and the MAP increased to 58.3 mm Hg ± 10.86 ($P < 0.001$), highlighting the additive value of this agent. Notably, the highest proportion of the patients in the current study developed mild hyponatremia (32.8%) compared to moderate (13.1%) and profound (7.5%) hyponatremia. The incidence and severity of the hyponatremia were independent of the vasopressin dose, $P = 0.25$ and $P = 0.56$ respectively. In the Baldasso et al., 2009, randomized trial, even low doses of vasopressin (0.005 units/kg/min) in critically ill children were associated with a high incidence of hyponatremia. However, a higher rate of hyponatremia was observed with higher doses (0.4 units/min) of vasopressin administered to patients with acute variceal hemorrhage (Kravetz et al., 1984).

It is worth mentioning that the surgical cardiac ($P = 0.049$) and non-cardiac ($P = 0.029$) patients had an increased incidence of hyponatremia compared to their counterparts. This may be attributed to the use of dextrose-containing hypotonic fluids as the maintenance fluid for pediatric patients post-cardiac surgery and isotonic fluids for fluid resuscitation that do not greatly affect the sodium levels (Table 6). An increased risk for hyponatremia has been observed in patients receiving hypotonic intravenous fluids perioperatively in multiple studies (Choong et al., 2011; Eulmesekian et al., 2010; Montañana et al., 2008, Yung and Keeley 2009). Similarly, exposure to CPB surgery predisposed the patients to hyponatremia ($P = 0.039$), mainly in the mild category ($P < 0.001$). This group has been reported with elevated endogenous vasopressin secretion (Mastropietro et al., 2010).

Even though BUN was significantly increased, it was still within range. A significant increase in the urinary output was observed at the end of therapy ($P < 0.001$), similar to the Davalos et al. clinical trial (Davalos et al., 2013). It is noteworthy that the vasoconstrictive doses of vasopressin can potentially increase urine output and decrease the serum creatinine, resulting in recovered renal perfusion and improved kidney function in hemodynamically unstable patients (Holmes et al., 2003). This supports an investigation in the true relationship between vasopressin and kidney function.

The requirement for hyponatremia treatment did not differ based on the severity of the hyponatremia ($P = 0.169$). The type of fluid used to treat hyponatremia did not differ significantly in terms of the severity of the hyponatremia, because the treatment varied according to the onset of the action (acute versus chronic). For acute and symptomatic hyponatremia, NaCl is usually administered as a repeated 2 mL/kg bolus of 3% NaCl, irrespective of the etiology of the hyponatremia (Moritz and Ayus 2010). Patients with hyponatremia do not always have deficient sodium levels, and administering sodium to hypervolemic hyponatremia, the hyponatremia may be corrected but it will result in a fluid overload. The fluid load is inherently risky in the neonatal period as it may lead to complications, including a patent ductus arteriosus, bronchopulmonary dysplasia, and necrotizing enterocolitis (Bockenhauer and Zieg, 2014). In this regard, 3% NaCl was never used in this study, with 0.45% and 0.9% NaCl most frequently used. More than half of the patients (58.5%) were placed on a continuous furosemide infusion. In addition to their cardiac benefits, the use of loop diuretics is usually recommended as a supplemental therapy with saline. Recently, vasopressin receptor II antagonists (AVPR2) have been approved for the treatment of patients with vasopressin-excess-induced hyponatremia (Lemmens-Gruber and Kamyar, 2006). The safety and efficacy of this indication have not been tested in neonates, as the concentrating capacity of neonates is impaired. Due to the ease of control over fluid administration in the NICU, fluid restriction is usually a sound option.

4.1. Limitations

We are aware of some limitations in our study, we acknowledge that the initiation, dose upgrading, and drug cessation is generally guided by an established clinical protocol, which ensure a consistent drug use in all patients, with the preserved clinical judgment of the attending physician. However, vasopressin, in some cases, was used out of protocol (early initiation or premature discontinuation) for some critically ill patients who responded abnormally. This may explain the number of patients excluded due to vasopressin administration for <24 h. Due to the retrospective nature of this study, with data obtained from a single hospital, it is possible that missing data or not clearly or incorrectly described is possible. The change in the vasopressin doses made it unclear which vasopressin dose caused the observed effect or if it was the accumulated dose. Some concurrently used drugs (loop diuretics, beta-blockers, corticosteroids, and ACE inhibitors) have the potential to cause hyponatremia, and others have a high-sodium content (e.g., meropenem and blood products) which was not accounted for, possibly confounding the findings. Some important hemodynamic data (e.g., cardiac output and systemic vascular resistance) and clinical consequences of hyponatremia were not investigated

in this study which may be of interest for clinicians when managing critically ill patients. An appropriate study design which confirms the causality association requires a comparator, which is lacking in our study. A prospective randomized study is required to provide evidence of the association of hyponatremia with vasopressin administration.

5. Conclusion

The use of vasopressin has been associated with decreased sodium levels, with an increased risk in cardiac surgery. The vasopressin dose did not significantly affect the incidence or severity of the hyponatremia. Continuous monitoring, correction of the level of sodium, and above all, the prevention of this phenomenon is indispensable to protect pediatric patients against more severe complications.

Funding

The authors received no financial support for authorship or publication of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None.

References

Agrawal, A., Singh, V.K., Varma, A., Sharma, R., 2012. Therapeutic applications of vasopressin in pediatric patients. Indian Pediatr. 49 (4), 297–305.
Alten, J.A., Borasino, S., Toms, R., Law, M.A., Moellinger, A., Dabal, R.J., 2012. Early initiation of arginine vasopressin infusion in neonates after complex cardiac surgery. Pediatric Crit. Care Med. 13 (3), 300–304.
Baldasso, E., Garcia, P.C.R., Piva, J.P., Branco, R.G., Tasker, R.C., 2009. Pilot safety study of low-dose vasopressin in non-septic critically ill children. Intensive Care Med. 35 (2), 355–359.
Bizzarri, C., Pedicelli, S., Cappa, M., Cianfarani, S., 2016. Water balance and 'salt Wasting'in the first year of life: the role of aldosterone-signaling defects. Hormone Res. Paediatrics 86 (3), 143–153.
Bockenhauer, D., Zieg, J., 2014. Electrolyte disorders. Clin. Perinatol. 41 (3), 575–590.
Choong, K., Arora, S., Cheng, J.I., Farrokhyar, F., Reddy, D., Thabane, L., Walton, J.M., 2011. Hypotonic versus isotonic maintenance fluids after surgery for children: a randomized controlled trial. Pediatrics 128 (5), 857–866.
Choong, K., Bohn, D., Fraser, D.D., Gaboury, I., Hutchison, J.S., Joffe, A.R., Litalien, C., Menon, K., McNamara, P., Ward, R.E., 2009. Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial. Am. J. Respir. Crit. Care Med. 180 (7), 632–639.
Davalos, M.C., Barrett, R., Seshadri, S., Walters III, H.L., Delius, R.E., Zidan, M., Mastropietro, C.W., 2013. Hyponatremia during arginine vasopressin therapy in children following cardiac surgery. Pediatric Crit. Care Med. 14 (3), 290–297.
Demiselle, J., Fage, N., Radermacher, P., Asfar, P., 2020. Vasopressin and its analogues in shock states: a review. Annals Intensive Care 10 (1), 1–7.
Donofrio, M.T., Massaro, A.N., 2010. Impact of congenital heart disease on brain development and neurodevelopmental outcome. Int. J. Pediatrics 2010.
Eulmesekian, P.G., Perez, A., Minces, P.G., Bohn, D., 2010. Hospital-acquired hyponatremia in postoperative pediatric patients: prospective observational study. Pediatric Crit. Care Med. 11 (4), 479–483.
Holmes, C.L., Landry, D.W., Granton, J.T., 2003. Science review: vasopressin and the cardiovascular system part 2–clinical physiology. Crit. Care 8 (1), 1–9.
Japundžić-Žigon, N., Lozić, M., Šarenac, O., Murphy, D., 2020. Vasopressin & oxytocin in control of the cardiovascular system: an updated review. Curr. Neuropharmacol. 18 (1), 14–33.
Jerath, N., Frndova, H., McCrindle, B.W., Gurofsky, R., Humpl, T., 2008. Clinical impact of vasopressin infusion on hemodynamics, liver and renal function in pediatric patients. Intensive Care Med. 34 (7), 1274–1280.
Kravetz, D., Bosch, J., Terés, J., Bruix, J., Rimola, A., Rodés, J., 1984. Comparison of intravenous somatostatin and vasopressin infusions in treatment of acute variceal hemorrhage. Hepatology 4 (3), 442–446.
Lechner, E., Hofer, A., Mair, R., Moosbauer, W., Sames-Dolzer, E., Tulzer, G., 2007. Arginine-vasopressin in neonates with vasodilatory shock after cardiopulmonary bypass. Eur. J. Pediatr. 166 (12), 1221–1227.
Lemmens-Gruber, R., Kamyar, M., 2006. Vasopressin antagonists. Cell. Mol. Life Sci. 63 (15), 1766–1779.
Massaro, A.N., El-Dib, M., Glass, P., Aly, H., 2008. Factors associated with adverse neurodevelopmental outcomes in infants with congenital heart disease. Brain Develop. 30 (7), 437–446.
Mastropietro, C.W., Clark, J.A., Delius, R.E., Walters III, H.L., Sarnaik, A.P., 2008. Arginine vasopressin to manage hypoxemic infants after stage I palliation of single ventricle lesions. Pediatric Crit. Care Med. 9 (5), 506–510.
Mastropietro, C.W., Rossi, N.F., Clark, J.A., Chen, H., Walters III, H., Delius, R., Lieh-Lai, M., Sarnaik, A.P., 2010. Relative deficiency of arginine vasopressin in children after cardiopulmonary bypass. Crit. Care Med. 38 (10), 2052–2058.
Obritsch, M.D., Bestul, D.J., Jung, R., Fish, D.N., MacLaren, R., 2004. The role of vasopressin in vasodilatory septic shock. Pharmacotherapy: The Journal of Human Pharmacology and Drug. Therapy 24 (8), 1050–1063.
Montanana, P.A., i Alapont, V.M., Ocón, A.P., López, P.O., Prats, J.L.L., Parreño, J.D.T., 2008. The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: a randomized, controlled open study. Pediatric Crit. Care Med. 9 (6), 589–597.
Moritz, M.L., Ayus, J.C., 2010. 100 cc 3% sodium chloride bolus: a novel treatment for hyponatremic encephalopathy. Metab. Brain Dis. 25 (1), 91–96.
Product Information: Vasostrict(TM) intravenous injection, vasopressin intravenous injection. Par Pharmaceutical Companies (per FDA), Spring Valley, NY, 2014.
Rhodes, A., Evans, L.E., Alhazzani, W., Levy, M.M., Antonelli, M., Ferrer, R., Kumar, A., Sevransky, J.E., Sprung, C.L., Nunnally, M.E., Rochwerg, B., 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 43 (3), 304–377.
Russell, J.A., Walley, K.R., Singer, J., Gordon, A.C., Hébert, P.C., Cooper, D.J., Holmes, C. L., Mehta, S., Granton, J.T., Storms, M.M., Cook, D.J., 2008. Vasopressin versus norepinephrine infusion in patients with septic shock. N. Engl. J. Med. 358 (9), 877–887.
Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., Decaux, G., Fenske, W., Hoorn, E.J., Ichai, C., Joannidis, M., 2014. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Nephrol. Dial. Transplant. 29 (suppl_2), i1–i39.
Verbalis, J.G., Goldsmith, S.R., Greenberg, A., Korzelius, C., Schrier, R.W., Sterns, R.H., Thompson, C.J., 2013. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am. J. Med. 126 (10), S1–S42.
Yung, M., Keeley, S., 2009. Randomised controlled trial of intravenous maintenance fluids. J. Paediatr. Child Health 45 (1–2), 9–14.