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CLINICAL RESEARCH ARTICLE

Post-operative dysnatremia is associated with adverse early outcomes after surgery for congenital heart disease

Andrea M. Ontaneda[1]✉, Jorge A. Coss-Bu[1], Curtis Kennedy[1], Ayse Akcan-Arikan[1,2], Ernesto Fernandez[1], Javier J. Lasa[1,3], Jack F. Price[1,3] and Lara S. Shekerdemian[1,3]

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BACKGROUND: Dysnatremia is a common disorder in critically ill surgical children. The study's aim is to determine the prevalence of dysnatremia and its association with outcomes after surgery for congenital heart disease (CHD).
METHODS: This is a single-center retrospective cohort study of children <18 years of age undergoing surgery for CHD between January 2012 and December 2014. Multivariable logistic regression analysis was used to evaluate the relationship between dysnatremia and outcomes during the perioperative period. A total of 1345 encounters met the inclusion criteria.
RESULTS: The prevalence of pre- and post-operative dysnatremia were 10.2% and 47.1%, respectively. Hyponatremia occurred in 19.1%, hypernatremia in 25.6%. Hypernatremia at 24, 48, and 72 h post-operative was associated with increased hospital mortality (odds ratios (OR) [95% confidence intervals (CI)] 3.08 [1.16–8.17], $p = 0.024$; 4.35 [1.58–12], $p = 0.0045$; 4.14 [1.32–12.97], $p = 0.0148$, respectively. Hypernatremia was associated with adverse neurological events 3.39 [1.12–10.23], $p = 0.0302$ at 48 h post-operative. Hyponatremia was not associated with any adverse outcome in our secondary analysis.
CONCLUSIONS: Post-operative dysnatremia is a common finding in this heterogeneous cohort of pediatric cardiac-surgical patients. Hypernatremia was more prevalent than hyponatremia and was associated with adverse early post-operative outcomes.

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IMPACT:

- Our study has shown that dysnatremia was highly prevalent in children after congenital heart surgery with hypernatremia associated with adverse outcomes including mortality.
- It is important to understand fluid and sodium regulation in the post-operative period in children with congenital heart disease to better address fluid overload and associated electrolyte imbalances and acute kidney injury.
- While clinicians are generally very aware of the importance of hyponatremia in critically ill children, similar attention should be given to hypernatremia in this population.

INTRODUCTION

Abnormalities of sodium balance (dysnatremia) are one of the most common electrolyte disorders in hospitalized patients. Dysnatremia has been defined as having a serum sodium lower than 135 mmol/l (hyponatremia) or higher than 145 mmol/l (hypernatremia), and has been associated with increased mortality and morbidity in adults admitted to intensive care.[1–11] Dysnatremia has been associated with increased infectious complications, coronary events and hospital mortality in adults after cardiac surgery[11–13] and is associated with increased hospital length of stay (LOS), morbidity and mortality in patients hospitalized with heart failure.[6,7,14]

Hyponatremia is observed in up to 25% of hospitalized children, and is in part attributed to the administration of hypotonic intravenous fluids.[15] This is further compounded by variable sodium losses and increased release of arginine vasopressin in children undergoing surgery and those with a critical illness.[2,16,17] A recent registered-based cohort study by Lehtiranta et al. of 46,518 acutely ill children reported an incidence of moderate to severe hypernatremia of 0.20%, and moderate to severe hyponatremia of 0.28%, concluding that severe dysnatremia was more prevalent in acutely ill children with underlying medical conditions and was markedly associated with the risk of death.[18] A study in young infants undergoing cardiac surgery suggested that hypernatremia was significantly associated with longer hospital length of stay, and duration of mechanical ventilation (MV).[19]

The aim of this study is to describe the prevalence of dysnatremia and its association with outcomes in infants and children after surgery for congenital heart disease (CHD).

[1]Division of Critical Care, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. [2]Division of Pediatric Nephrology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. [3]Division of Pediatric Cardiology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA. ✉email: amontan1@texaschildrens.org

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MATERIAL AND METHODS

Patients

Retrospective cohort review of all children admitted to Texas Children's Hospital Cardiac Intensive Care Unit (CICU) after surgery for CHD between January 2012 and December 2014. During this period there were 2052 surgical encounters for CHD surgery, of which 707 were excluded according to the following criteria: age 18 years or older, prematurity (completed gestational age equal to or less than 37 completed weeks at the time of surgery), patients with ventricular assist device, and lack of sodium level before surgery. A total of 1345 surgical encounters in 1198 patients are included in this review. Each encounter was assigned and analyzed as a different unique identifier.

The primary outcome of this study was mortality, and secondary outcomes were neurological events (seizures and stroke), acute kidney injury (AKI), and hospital LOS.

Clinical data and laboratory values

Patient data were collected from the electronic medical record (EMR) and institutional Congenital Heart Surgical database. Data collected included age, sex, weight, type of surgery, Risk Adjustment for Congenital Heart Surgery Score (RACHS-1) classification (low: categories 1–3, or high: categories 4–6),[20] cardiopulmonary bypass (CPB) and cross clamp (CC) times, hospital LOS and duration of MV. Pre-operative and daily creatinine values were collected for each encounter and AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline[21] as an increase in serum creatinine to equal or greater than 1.5 times baseline. Total diuretic dose (mg/kg), vasopressin dose, daily fluid balance, and use of peritoneal dialysis (PD) were recorded during the first 72 h. To evaluate the effect of total diuretic exposure on dysnatremia, the total diuretic dose that included one or more diuretic during the first 72 h used was calculated.

Sodium values

We defined dysnatremia as either hyponatremia (serum sodium <135 mmol/l), or hypernatremia (serum sodium >145 mmol/l). Normonatremia was defined as serum sodium levels between 135 and 145 mmol/l. Sodium values were obtained from the EMR at the following time points: prior to surgery, and for the first 72 h thereafter. Sodium values were included from the chemistry panel analyzed by the laboratory and excluded when analyzed by point-of-care methods. The peak and trough sodium levels for each 24-h period were documented. If the peak and trough values were both within the normal range, the first value of the day was chosen to represent each 24-h period. Encounters were categorized into normonatremia, hyponatremia, or hypernatremia based on their sodium levels at 24, 48 and 72 h post-operative. None of the encounters had both hyponatremia and hypernatremia in the same 24-h period.

Statistical analysis

Continuous variables were expressed as mean and standard deviation if they were normally distributed, and median with interquartile ranges (IQR 25th–75th) if they were not normally distributed and analyzed with unpair *t*-test and Mann–Whitney *U* test, respectively. Pearson's χ^2 or Fisher's exact test was used to determine differences between groups of categorical variables. Univariate analyses examining the associations between each covariate and hypernatremia, hyponatremia, AKI, use of diuretics, PD, mortality, hospital LOS, MV duration, and adverse neurological event was used. Multivariable logistic regression analysis was used to test for independent predictors of dysnatremia and other outcome variables. In addition, using multivariable logistic regression analysis, the odds ratios for mortality and AKI were calculated using the normonatremia group as the reference versus dysnatremia groups (hypernatremia and hyponatremia). All variables with $p \le 0.10$ on univariate analysis were included in the multivariable analyses. Statistical significance was established a priori as $p < 0.05$. Statistical analysis was performed with Stat View Version 5.0.1 (SAS Institute Inc, Cary, NC).

RESULTS

During the study period, there were 2052 surgical encounters for CHD surgery, of which 707 were excluded and 1345 encounters (1198 patients) were included (Fig. 1). The median age of the cohort was 10 months (2.7–60.1) of whom 52.5% were aged 1 year or less. The majority were male, and 86.5% of patients were in RACHS-1 categories 1–3. Patient surgical data are listed in Table 1.

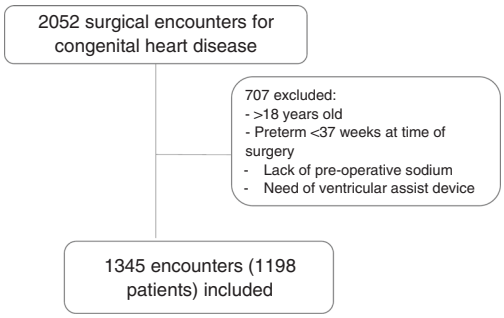

Fig. 1 Flowchart of the study cohort.

Table 1. Patient demographics and operative details.

Variable	Encounters ($n = 1345$)
Age, months	10 (2.7–60.1)
Neonate (0–30 days), *n* (%)	240 (17.8)
Infant (1–12 months), *n* (%)	466 (34.7)
Toddler (1–3 years), *n* (%)	149 (11.1)
Child (3–17 years), *n* (%)	490 (36.4)
Sex	
Female, *n* (%)	594 (44.2)
Male, *n* (%)	751 (55.8)
Weight, kg	8.1 (4.5–17.9)
Risk adjustment for congenital heart surgery (RACHS-1)	
1–3, *n* (%)	1163 (86.5)
4–6, *n* (%)	182 (13.5)
Hospital length of stay, days	8 (5–15)
Duration of mechanical ventilation, h	23.9 (7.1–59.3)
Cardiopulmonary bypass encounters, *n* (%)	1177 (87.5)
Cardiopulmonary bypass time, min	138 (92–192)
Cross clamp time, min	77 (38–121)
Pre-operative sodium, mmol/l ($n = 1345$)	139 ± 3
24 h post-operative sodium, mmol/l ($n = 1344$)	142 ± 4
48 h post-operative sodium, mmol/l ($n = 1246$)	140 ± 4
72 h post-operative sodium, mmol/l ($n = 1120$)	139 ± 4
Mortality (patients $n = 1198$), *n* (%)	24 (2.0)

Values are median (IQR 25th–75th) and mean ± standard deviation.

Prevalence of dysnatremia

The overall prevalence of pre-operative hyponatremia and hypernatremia were 8.7% and 1.5%, respectively (Table 2). Dysnatremia was present in 47.1% of children during the first 72 h after surgery. The prevalence of post-operative hyponatremia was 19.1%, and post-operative hypernatremia was 25.6%. The occurrence of both hypo and hypernatremia within a single encounter was rare, in only 2.4%. When comparing infants aged less than 1 year with older children, the prevalence of hypernatremia at 24, 48 and 72 h was 24.2%, 12.8% and 10.2%, respectively (all $p < 0.01$). Important sodium values shifts were evidenced with an increase of hypernatremia from 1.5% in the

Table 2. Prevalence of dysnatremia.

Prevalence, *n* (%)	Dysnatremia	Hyponatremia	Hypernatremia
Pre-operative sodium (total 1345), *n* (%)	137 (10.2)	117 (8.7)	20 (1.5)
24 h post-operative sodium (total 1344), *n* (%)	382 (28.4)	90 (6.7)	292 (21.7)
48 h post-operative sodium (total 1246), *n* (%)	255 (20.5)	131 (10.5)	124 (9.9)
72 h post-operative sodium (total 1120), *n* (%)	247 (22)	156 (13.9)	91 (8.1)
Pre-operative sodium			
Neonate, *n* (%)		34 (29.1)	3 (15)
Infant, *n* (%)		70 (59.8)	7 (35)
Toddler, *n* (%)		7 (6)	1 (5)
Child, *n* (%)		6 (5.1)	9 (45)
24 h post-operative sodium			
Neonate, *n* (%)		22 (24.5)	63 (21.6)
Infant, *n* (%)		36 (40)	108 (37)
Toddler, *n* (%)		9 (10)	30 (10.3)
Child, *n* (%)		23 (25.5)	91 (31.1)
48 h post-operative sodium			
Neonate, *n* (%)		20 (15.3)	24 (19.4)
Infant, *n* (%)		41 (31.3)	65 (52.4)
Toddler, *n* (%)		10 (7.6)	6 (4.8)
Child, *n* (%)		60 (45.8)	29 (23.4)
72 h post-operative sodium			
Neonate, *n* (%)		33 (21.1)	16 (17.6)
Infant, *n* (%)		60 (38.5)	52 (57.1)
Toddler, *n* (%)		9 (5.8)	9 (9.9)
Child, *n* (%)		54 (34.6)	14 (15.4)

Neonate (0–30 days), infant (1–12 months), toddler (1–3 years), child (3–17 years).

pre-operative period to 21.7% at 24 h post-operative ($p < 0.001$), and pre-operative hyponatremia from 8.7% to 13.9% at 72 h ($p < 0.01$).

Dysnatremia and outcomes

Mortality. Twenty-four patients (2.0%) died before hospital discharge. Younger age, lower weight, increased CPB, hospital LOS, and MV times were associated with hospital mortality (Table 3). By univariate logistic regression analysis, higher surgical complexity was associated with mortality (OR 6.42 [3.04–13.53], $p < 0.0001$).

Association of mortality and sodium category at 24, 48 and 72 h after surgery is shown in Table 4. In a multivariable logistic regression analysis controlling for age, RACHS-1, and CPB time, post-operative hypernatremia at 24 h (OR 3.08 [1.16–8.17], $p = 0.024$), 48 h (OR 4.35 [1.58–12], $p = 0.0045$); and 72 h (OR 4.14 [1.32–12.97], $p = 0.0148$) were associated with mortality. Hyponatremia was not associated with an increased risk of mortality at any time point.

Cumulative fluid balance per kilogram at 72 h post-operative was higher in the patients who did not survive [median (IQR) +170.95 ml/kg (+10.51 to +309.68) vs +3.67 ml/kg (–7.89 to +30.26), $p < 0.0001$]. Two-third of patients who died had received PD.

Neurological events. Twenty-one patients (1.56%) had adverse neurological events during their hospital stay (neonates = 8, infant = 5, toddler = 3, child = 5). Stroke was observed in 7 patients, seizures in 9, and both stroke and seizures in 5 patients. In a univariate logistic regression analysis, hypernatremia was associated with adverse neurological events at 24 h (OR 4.5 [1.9–10.9], $p = 0.0007$) and 48 h (OR 4.2 [1.65–10.6], $p = 0.0025$) after surgery. In a multivariable logistic regression analysis controlling for age, CPB time, and RACHS-1, hypernatremia at 48 h post-operative (OR 3.39 [1.12–10.23], $p = 0.0302$) was associated with adverse neurological events. Hyponatremia was not associated with an increased risk of adverse neurological events at any time point.

Acute kidney injury. Acute kidney injury was present in 149 (12.8%), 59 (5.6%) and 28 (3.1%) of the encounters at 24 ($n = 1159$), 48 ($n = 1051$) and 72 ($n = 898$) hours after surgery, respectively. Increased CPB, CC and MV times, at all post-operative time points, were significantly associated with AKI. At 24 h after surgery, a more positive net fluid balance ($p = 0.0036$), and hypernatremia ($p = 0.0002$) were associated with AKI. At 48 h post-operative, younger age and lower weight, increased hospital LOS, a more positive net fluid balance, PD use, and hypernatremia were associated with AKI ($p < 0.05$) (Table 5). The use of more than one diuretic class at any of the post-operative time points was not associated with AKI; however, a total furosemide dose of more than 10 mg/kg was found to be associated with AKI (OR 3.44 [1.26–9.41], $p = 0.016$). Association of AKI with sodium category at 24, 48 and 72 h after surgery is described in Table 6. In a multivariable logistic regression analysis controlling for age, hospital LOS, CPB time, CC time, MV time, and net fluid balance; hypernatremia at 48 h post-operative (OR 3.84 [2.02–7.29], $p < 0.0001$) was associated with AKI. Hyponatremia was not associated with AKI at any time point.

Dysnatremia and other factors

Vasopressin. Vasopressin infusion was used in 240 encounters (at any time during the first 72 h) and was associated with

Table 3. Mortality and neurological event.

Variable	Outcome		Neurological event	
	Survived	Died	No	Yes
Age, months	15.1 (2.6–71)	1.5 (0.30–5.9)*	10 (2.8–60)	4.2 (0.35–38)
	($n = 1174$)	($n = 24$)	($n = 1324$)	($n = 21$)
Weight, kg	9.2 (4.4–19)	4.2 (2.9–5.8)*	8.1 (4.5–17.9)	4.5 (3.3–13.3)
	($n = 1174$)	($n = 24$)	($n = 1324$)	($n = 21$)
Hospital LOS, days	8 (5–14)	41 (19–72)*	8 (5–15)	57 (11.8–112)*
	($n = 1174$)	($n = 24$)	($n = 1324$)	($n = 21$)
CPB time, min	137 (92–190)	185 (156–258)*	138 (92–191)	175 (148–253)*
	($n = 1014$)	($n = 19$)	($n = 1149$)	($n = 20$)
Cross Clamp Time, min	79 (43–121)	98 (40–132)	77 (37–121)	96 (79–121)
	($n = 1013$)	($n = 19$)	($n = 1147$)	($n = 20$)
Duration of MV, h	22.7 (6.8–55.2)	266 (122–764)*	24 (7–56)	226 (64–501)*
	($n = 1125$)	($n = 18$)	($n = 1246$)	($n = 21$)
Pre-op sodium, mmol/l	139 ± 3	139 ± 6	139 ± 3	139 ± 4
	($n = 1174$)	($n = 24$)	($n = 1324$)	($n = 21$)
24 h sodium, mmol/l	142 ± 4	145 ± 6**	142 ± 4	145 ± 4**
	($n = 1173$)	($n = 24$)	($n = 1323$)	($n = 21$)
48 h sodium, mmol/l	139 ± 4	144 ± 5**	140 ± 4	144 ± 4**
	($n = 1078$)	($n = 23$)	($n = 1226$)	($n = 21$)
72 h sodium, mmol/l	139 ± 4	142 ± 6**	139 ± 4	140 ± 4
	($n = 956$)	($n = 22$)	($n = 1100$)	($n = 21$)

Values are median (IQR 25th–75th) and mean ± standard deviation.
LOS length of stay, *CPB* cardiopulmonary bypass, *MV* mechanical ventilation.
*$p < 0.05$ by Mann–Whitney test.
**$p < 0.05$ by unpair *t*-test.

Table 4. Association of mortality and sodium category at 24, 48, and 72 h after surgery.

	Survived	Died	OR (95% CI)	*p*
Sodium category at 24 h ($n = 1198$)	*n* (%)	*n* (%)		
Normonatremia	863 (73.6)	11 (45.8)	1	
Hyponatremia	74 (6.3)	1 (4.2)	1.06 (0.14–8.3)	0.96
Hypernatremia	236 (20.1)	12 (50)	3.98 (1.74–9.2)	0.0011
Sodium category at 48 h ($n = 1101$)				
Normonatremia	864 (80.2)	13 (56.5)	1	
Hyponatremia	117 (10.9)	1 (4.4)	0.56 (0.07–4.38)	0.59
Hypernatremia	97 (8.9)	9 (39.1)	6.16 (2.56–14.8)	<0.0001
Sodium category at 72 h ($n = 979$)				
Normonatremia	760 (79.5)	13 (56.5)	1	
Hyponatremia	131 (13.7)	3 (13.1)	1.34 (0.37–4.76)	0.65
Hypernatremia	65 (6.8)	7 (30.4)	6.29 (2.43–16.3)	0.0002

OR odds ratios for mortality are vs. normonatremia group as a reference, *CI* confidence interval.

hypernatremia at 24 h (OR 2.44 [1.78–3.33], $p < 0.0001$), 48 h (OR 2.95 [1.98–4.38], $p < 0.0001$, and 72 h after surgery (OR 2.9 [1.85–4.55], $p < 0.0001$).

Fluid balance. The median (IQR) net fluid balances for all encounters at 24, 48 and 72 h after surgery were +9.4 ml/kg (–8.1 to +52.1), +5.4 ml/kg (–13.7 to +42.8), and +1.7 ml/kg (–15.7 to +21.8), respectively. The median (IQR) net fluid balance (ml/kg) in the normonatremia group at 24, 48, and 72 h post-operative was +6.2 (–9.2 to +39.8); +6.4 (–13.5 to +54.7); and +2.3 (–16.3 to +22.1), respectively. In the hyponatremia group at 24, 48, and 72 h post-operative, the net fluid balance (ml/kg) was +18.1 (–5.6 to +60); +1 (–13.8 to +20.9); and –1.02 (–19.3 to +25), respectively; and in the hypernatremia group was +21.3 (–4.7 to +243.6); +10.6 (–12.4 to +233), and –1.3 (–16.4 to +41.7) ml/kg, respectively. There was no significant difference in net fluid balance between normonatremia vs hyponatremia groups at any time point, whereas the net balance was significantly more

Table 5. Factors associated with acute kidney injury (AKI) in the first 72 h after surgery.

Variable	24 h ($n = 1159$)		48 h ($n = 1051$)		72 h ($n = 898$)	
	AKI		AKI		AKI	
	Yes ($n = 149$)	No ($n = 1010$)	Yes ($n = 59$)	No ($n = 992$)	Yes ($n = 28$)	No ($n = 870$)
AKI incidence, *n* (%)	149 (12.8)		59 (5.6)		28 (3.1)	
Age, months	7.2 (3.9–48)	19.3 (3.2–72)	6.2 (3.5–10)*	11.2 (2.8–65)	6.8 (5.2–68)	7.3 (2.4–54)
Weight, kg	6.7 (5.1–16)	10.2 (4.8–19)	6.1 (4.6–9)*	8.4 (4.6–18)	6.9 (5.7–22)	7.1 (4.2–17)
Hospital length of stay, days	8 (6–15)	7 (5–13)	14 (9–29)*	8 (5–14)	15.5 (9.5–34)*	9 (6–16)
Cardiopulmonary bypass time, min	184 (122–254)*	132 (90–183)	216 (166.5–272)*	139 (96.3–190)	222.5 (131–308)*	150 (100–200)
Cross clamp time, min	120 (75–156)*	74 (37–112)	130.5 (96–169)*	80 (44–121)	129 (71–176)*	86 (50.5–126)
Mechanical ventilation duration, h	30.5 (15–86)*	18.6 (6.6–50)	83.7 (31–176)*	23.5 (7.3–53)	78.8 (30–223)*	26.7 (8.4–74)
RACHS-1						
1–3, *n* (%)	133 (13.1)	885 (86.9)	51 (5.5)	863 (94.5)	24 (3.1)	743 (96.9)
4–6, *n* (%)	16 (11.4)	124 (88.6)	8 (5.9)	128 (94.1)	4 (3)	130 (97)
Net fluid balance (ml/kg)	15.2 (–1.2 to 57)*	6.3 (–10 to 37.6)	26.1 (–11 to 366)*	4.3 (–14 to 34)	1.5 (–21 to 39)	2.8 (–16 to 23)
Peritoneal dialysis, *n* (%)	41 (16.5)	208 (83.5)	27 (10.9)**	220 (89.1)	10 (4.1)	233 (95.9)
Diuretics: 1 class, *n* (%)					15 (2.5)	575 (97.5)
Diuretics: 2 classes, *n* (%)					9 (5.2)	164 (94.8)
Diuretics: 3 or more classes, *n* (%)					1 (2.6)	38 (97.4)

Values are median (IQR 25th–75th).
RACHS-1 risk adjustment for congenital heart surgery. Diuretics analysis was done only at 72 h.
*$p < 0.05$ by Mann–Whitney test.
**$p < 0.05$ by χ^2.

Table 6. Association of AKI and sodium category at 24, 48, and 72 h after surgery.

	No AKI	AKI	OR (95% CI)	*p*
Sodium category at 24 h ($n = 1159$)	*n* (%)	*n* (%)		
Normonatremia	756 (74.8)	94 (63.1)	1	
Hyponatremia	66 (6.5)	7 (4.7)	0.85 (0.38–1.91)	0.69
Hypernatremia	188 (18.6)	48 (32.2)	2.05 (1.40–3.01)	0.0002
Sodium category at 48 h ($n = 1051$)				
Normonatremia	805 (81.1)	33 (55.9)	1	
Hyponatremia	112 (11.3)	3 (5.1)	0.65 (0.19–2.16)	0.48
Hypernatremia	75 (7.6)	23 (39)	7.48 (4.17–13.4)	<0.0001
Sodium category at 72 h ($n = 898$)				
Normonatremia	688 (79.1)	19 (67.8)	1	
Hyponatremia	123 (14.1)	4 (14.3)	1.17 (0.39–3.52)	0.65
Hypernatremia	59 (6.8)	5 (17.9)	3.07 (1.11–8.51)	0.0313

OR odds ratios for AKI (acute kidney injury) are vs. normonatremia group as a reference, *CI* confidence interval.

positive at all three time points in the hypernatremic vs normonatremic group (all $p < 0.01$). When comparing hyponatremia and hypernatremia groups the only significant difference in net fluid balance was at 72 h ($p < 0.05$).

Peritoneal dialysis. In newborns and younger infants, PD was used for control of fluid balance in preference to diuretics during the first 24–48 h after surgery. PD was used in 350 encounters (26%) with a median age of 1.2 (0.23–3.9) months and weight of 3.9 (3.3–5.6) kg. In a univariate logistic regression analysis, younger age; lower weight; increased hospital length of stay, CPB, CC and MV times; and higher complexity, were associated with PD use (all $p < 0.05$). PD use was associated with hypernatremia at 48 h (OR 2.34 [1.6–3.4], $p < 0.0001$, and 72 h after surgery (OR 2.2 [1.4–3.38], $p = 0.0004$). In a multivariable logistic regression analysis controlling for age, CPB time, CC time, RACHS-1 and MV time; PD use was not associated with dysnatremia at 48 or 72 h post-operative.

Diuretics. Diuretic use during the first 72 h after surgery, according to the class of diuretic, was as follows: one class in 63%, 2 classes in 17.8% and 3 or more classes in 4.1%. The most commonly used diuretic was furosemide (in 81.6% of encounters

with diuretic use). We further classified the total dose of furosemide (intravenous and enteral) over the first 72 h after surgery, into three different categories: <5 mg/kg; 5–10 mg/kg; and >10 mg/kg. The median (IQR) total doses of furosemide at 72 h were 3 mg/kg (0.76–6.7); 3.1 mg/kg (1–6.9) and 5.4 mg/kg (2.1–10.7) for the normonatremic, hyponatremic and hypernatremic encounters, respectively. In a univariate analysis, a total cumulative dose of furosemide of greater than 10 mg/kg during the first 72 h after surgery, was associated with hypernatremia ($p < 0.0001$). There was no association with hyponatremia.

In a multivariable logistic regression analysis, controlling for vasopressin use and net daily fluid balance; the use of three or more classes of diuretics (OR 3.4 [1.68–6.9], $p = 0.0007$), and the use of three or more classes of diuretics plus PD (OR 3.6 [1.17–10.9], $p = 0.025$) were associated with hypernatremia at 72 h after surgery.

DISCUSSION

Our study examined dysnatremia in pediatric patients after surgery for CHD. Dysnatremia was present in 47% of pediatric patients during the first 72 h after cardiac surgery, with hypernatremia being more common than hyponatremia. In addition, we have shown that hypernatremia, but not hyponatremia, was associated with worse post-operative outcomes.

Dysnatremia has been reported in up to a third of critically ill adults.[1,3,9] Our observed prevalence of dysnatremia affecting 47% of all pediatric cardiac-surgical encounters is substantially higher than in any other subgroup studied to date. In the existing literature, in contrast to hyponatremia in hospitalized children, for which there is a substantial body of literature, there are very few studies examining hypernatremia and its association with outcomes in the pediatric population. Hyponatremia is commonly reported in hospitalized and critically ill children.[15,16,22,23] In our study we found that hypernatremia (25.6%) was more prevalent than hyponatremia (19.1%) in the first 72 h after cardiac surgery.

The etiology of dysnatremia after pediatric cardiac surgery is likely to be multifactorial. Some of the potential contributors to this include CPB itself which may induce natriuresis;[24] intraoperative fluid removal with various modes of ultrafiltration; the choice and regimen for perioperative intravenous fluids (hypotonic or isotonic); fluid resuscitation; management of fluid balance; diuretic therapy; PD use; administration of fluids or drugs with a higher sodium content such as albumin 5% or sodium bicarbonate; or impaired water excretion due to antidiuretic hormone release or vasopressin use.

In our institution and many others, the CPB strategy for patients who undergo cardiac surgery includes intraoperative ultrafiltration as well as early post-operative fluid restriction for the first 72 h, which may contribute to the high prevalence of early hypernatremia. Lee et al. studied acute serum sodium concentration changes in pediatric patients after CPB, and found that hypernatremia was present in one-third of the patients at the conclusion of CPB, and was associated with longer hospital LOS and higher morbidity rates.[25] Moreover, while we generally avoid diuretic therapy during the first 24 h, in the youngest infants—peritoneal dialysis is often the preferred approach to control fluid balance.

The prevalence of hypernatremia fell at 48 and 72 h, with a concomitant increase in hyponatremia, which predominated at 72 h. Again, this may be linked in part to the routine practice of liberalizing fluids, increasing the use of diuretics, and starting nutrition during this time frame. However, we did not find an association between total cumulative diuretic use and hyponatremia. Instead, the highest cumulative doses of furosemide (>10 mg/kg), and the use of three or more diuretic classes, were both associated with hypernatremia at 72 h after surgery.

There were some important unexpected associations in our population that are at odds with some of the existing literature in children after cardiac surgery. These include the association of both PD and vasopressin with hypernatremia. While others have found the use of PD to be associated with hyponatremia[26] we found that the converse was true in our population in univariate analysis; however, this was not found in multivariable logistic regression analysis and the reason for this is not clear. Our practice is to utilize a personalized PD with a starting dextrose concentration of 1.5%, and a sodium concentration of 132 mmol/l. Similarly, our observation of an association between the use of vasopressin and hypernatremia at all time points after surgery differs from others who have reported hyponatremia with its use.[17]

AKI has been reported in up to 25% of children after cardiac surgery, and has been associated with longer hospital stays and higher mortality.[27–30] While there was no association between AKI and mortality in our cohort, we found that hypernatremia was associated with AKI. As reported in the literature, it was also associated with poor prognostic factors such as increased hospital LOS, CPB and MV times.

One of the most serious, and often irreversible complications of dysnatremia is an acute brain injury. Hyponatremic encephalopathy, and vascular thrombosis and intracranial hemorrhages directly attributable to hypernatremia, can result in death or permanent neurological injury in children.[31] Adverse neurological events occurred in 1.56 % of our patients and were associated with hypernatremia at 48 h after surgery. While these were not clinically identified during the first 72 h after cardiac surgery, the precise timing of neurological insults cannot be clearly ascertained.

Multiple studies in the adult population have described high mortality rates in patients with dysnatremia.[4,6–10] A recent study in acutely ill children found a marked association between severe dysnatremia and risk of death.[18] Our mortality rate was 2.0% and was associated with post-operative hypernatremia at all time points after surgery.

Our study had a major limitation which was the age of the database creation. Several other significant limitations include the retrospective nature that limited our access to some of the details, such as the ability to accurately record the exact nature and rate of intravenous crystalloids, sodium bicarbonate, and enteral or parenteral nutrition, which are highly variable sources of exogenous sodium and water. Moreover, drug diluents, drug boluses, intravenous or intra-arterial “flushes” are just a handful of examples of additional sodium and/or water that could contribute to the genesis of dysnatremia. Another major limitation of our study is the lack of the quantification of intraoperative modified ultrafiltration and fluid balance. Daily weights would have been of interest in this review. While daily weights are generally routine in the post-operative setting, it may not be possible during the first days after surgery due to actual or potential instability. Another limitation is that some aspects of perioperative care have evolved over the last decade; however, our observations are consistent with what has been reported in the literature. In addition, while the observation of the association between dysnatremia and neurological events is likely to be of relevance, the exact timing of the neurological insult for the majority, was unknown. Therefore, we cannot speak whether dyanatremia predated or it is likely the cause of the neurological events.

CONCLUSIONS

Post-operative dysnatremia is a common finding in this single-center analysis of pediatric cardiac-surgical patients. Hypernatremia is more prevalent than hyponatremia and is associated with worse post-operative outcomes. While clinicians are generally very aware of the importance of hyponatremia in critically ill children, similar attention should be given to hypernatremia in this

population. This warrants further evaluation in a prospective study.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved with a waiver of consent by the Baylor College of Medicine Institutional Review Board and given approval number H-38048 on July 10, 2016.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to Andrea M. Ontaneda.

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