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Serum chloride and serum sodium derangements in children on prolonged furosemide therapy and their effect on diuretic response

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Abstract

Background: Electrolyte disturbances are not uncommon in patients on chronic furosemide therapy. We hypothesized that serum chloride (Cl) and serum sodium (Na) abnormalities may occur in children on prolonged furosemide therapy affecting the diuretic response in these children.

Methods: The study included 45 children, with congenital left to right shunts causing chronic congestive state which necessitated chronic furosemide therapy. Patients in need to an increase of their furosemide dose were recruited in the study. We assessed serum Cl and serum Na as well as parameters of diuretic responsiveness; net fluid output and change in body weight/40 mg furosemide, and change in urinary Na/K ratio. These parameters were assessed initially and at day 3 after increasing furosemide dose.

Results: According to serum levels of Cl and Na, patients were divided into four groups: isolated hyponatremia (15 patients, 33.3%), isolated hypochloremia (9 patients, 20%), combined hypochloremia and hyponatremia (12 patients, 26.7%), and normal serum electrolytes (9 patients, 20%). Patients with combined hyponatremia and hypochloremia and those with isolated hypochloremia showed minimal clinical and radiological signs of decongestion as well as lowest changes in urinary Na/K ratio, fluid output and weight change/40 mg furosemide on augmenting the diuretic dose, unlike the hyponatremic patients who had near normal parameters with no evidence of diuretic resistance.

Conclusion: Both hypochloremia and hyponatremia are common in patients on prolonged furosemide therapy. Hypochloremia is associated with a poor diuretic response, unlike isolated hyponatremia which does not seem to affect the diuretic response. Concomitant occurrence of hyponatremia and hypochloremia is associated with poor diuretic response as well which can be worse than that seen in isolated hypochloremia.

Keywords: Pediatric, Heart failure, Furosemide, Diuretic resistance, Hyponatremia, Hypochloremia

Background

Fluid overload, clinically evident as systemic and/or pulmonary congestion, frequently occurs in children with congenital heart disease and exerts a major negative prognostic impact [1]. Adequate control of systemic congestion along with maintenance and improvement of renal function represents a key target of patient management [2]. The current guidelines suggest that decongestion

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should be attempted through diuretic therapy. Diuretics, essentially loop diuretics, are utilized in more than 90% of patients with congestive state to increase urinary output, and to achieve dyspnea relief and weight loss [3].

Ineffective diuretic treatment of systemic and pulmonary congestion is commonly referred to as diuretic resistance or refractoriness. It is thought that about one third of patients with HF, especially during acute decompensation, may present with apparent diuretic refractoriness [4].

Accumulating evidence has shown that Serum chloride is highly important in the cardio-renal processes. Notably, chloride is responsible for modulation of renin secretion and tubular glomerular feedback**.** Furthermore, recent evidence suggests an association between chloride and diuretic response [5].

Diuretics are a common cause of drug induced hyponatremia [6], which can be considered a marker of neurohormonal activation that reflects the severity of heart failure [7]. Hyponatremic subjects often have inappropriately elevated plasma arginine vasopressin (AVP) levels which leads to enhanced renal water retention by increasing the number of aquaporin water channels in the collecting duct of the kidney [8].

The aim of our study was to highlight possible serum Cl and Na derangements in patients on prolonged furosemide therapy and to investigate the effect of these derangements on the diuretic response in these patients.

Methods

This was a prospective study that was carried out at Ain Shams University Children's Hospital during the period from June 2020 to December 2020, including 45 patients with congenital left to right shunts on chronic furosemide therapy as a single diuretic agent, requiring an increase in their diuretic dose due to uncontrolled congestive symptoms despite normal systolic functions of the heart.

Study population and methodology

The study included 45 patients $\leq$ 18 years old with chronic pulmonary and/or systemic venous congestion and normal systolic function of the heart. Congestive state in these patients was defined as the presence of signs or symptoms of volume overload as tachypnea and other features of respiratory distress like grunting and nasal flaring in infants, retractions and use of accessory muscles, wheezing or rales in older children in absence of any evidence of pulmonary infection. In addition to features of systemic congestion, which include hepatomegaly, and peripheral edema [9].

Patients presenting without prior furosemide therapy or multiple diuretic agents, those with low ejection fraction heart failure and patients with significant co-morbidities including renal impairment or renal replacement therapy were excluded.

Sample size and method

The study group included children fulfilling the inclusion criteria. Patients were assessed clinically, radiologically, and laboratory wise initially and on day 3 of diuretic adjustments.

All patients were clinically assessed by full history taking, general and local cardiac examination.

Laboratory investigations included the following

Samples were collected for serum measurements of sodium, potassium, and chloride on day 1 and day 3 of therapy. Bicarbonate, blood urea nitrogen, and creatinine were sampled as well to ensure normal kidney functions. Two milliliters of venous blood were withdrawn under aseptic condition. Serum was separated by centrifugation at $3000\times g$ for 15 min for immediate assay of blood chemistry. Sodium and potassium concentrations were measured in milliequivalents per liter (mEq/L) using ion specific electrode (ISE) technique using Beckman Coulter Analyzers**.**

Hyponatremia was considered as serum sodium concentration less than or equal to 130 mEq/L [10]. Hypochloremia was considered as serum chloride level less than or equal to 95 mEq/L [11].

For urinary Na/k ratio, random urine samples were collected from all subjects in sterile containers and centrifuged for 20 min at the speed of 2000–3000 rotation per minute. The supernatant was separated in aliquots and stored at 20 °C till subsequent assay of sodium and potassium. Day 3 values of Na/K ratio were compared to that of day 1. An increase in urinary Na/K ratio was considered as improved natriuresis and diuresis.

On day 1 as well as day 3, 24-h urine collections were conducted. Caregivers of participants were instructed to collect all urine output using a measuring cup or urine bag for smaller infants, with all urine saved in 2 L bottles. To avoid under- and overcollection, the start and end times of the 24-h urine collection were supervised by clinic staff.

All fluids taken by the patients over the 24-h interval were strictly calculated to determine total fluid intake. Net fluid output calculation was done by subtracting the fluid intake from the 24-h urine output of the patients. This was further divided by the dose of furosemide given to determine net fluid output/40 mg furosemide.

Forty milligrams of furosemide equivalents was chosen as reference because this dose has been reported to produce near-maximal rate of instantaneous natriuresis in healthy volunteers naive to diuretics [12].

Weight was recorded for all patients in kilogram. This was measured using electronic scales with the child clothed with minimum clothes and without shoes. All patients were weighted initially and on day 3 of therapy. Change in body weight/40 mg furosemide was calculated.

Chest X-ray (CXR) with details of cardiothoracic ratio (CTR) as well as radiological evidence of pulmonary plethora or edema was done in all patients.

Echocardiography in supine position using General Electric (Vivid-E9) system with probe 5S/ or 6S MHz (multifrequency transducer) according to age of patient was done to confirm the underlying congenital cardiac disease as well as assessment of systolic functions.

According to serum levels of chloride and sodium, patients were divided into four groups: isolated hypochloremia, isolated hyponatremia, combined hypochloremia and hyponatremia, and patients with normal serum chloride and sodium.

Statistical methodology

Statistical analysis was performed with Statistical package for social science (SPSS). Numerical data was summarized using means and standard deviations or medians and ranges. Correlation between variables was evaluated using Pearson's correlation coefficient. P values < 0.05 was considered statistically significant.

Results

Forty-five patients were included in the current study. All patients had congenital left to right cardiac shunting with different combinations of atrial and ventricular septal defects, Ductus arteriosus, and AV canal defects. All patients had chronic pulmonary and/or systemic venous congestion which mandated long-term furosemide therapy.

Median age of the patients was 0.75 years (range 0.2–6 years), with 27 (60%) male patients and 18 (40%) female patients. Mean initial weight of 5.64 ± 2.74 kg, with mean height of 69.13 ± 16.66 cm and mean BMI of 13.39 ± 4.21. Median duration of furosemide therapy was 9.5 months (Table 1).

On assessment of serum chloride and sodium in the studied population, we have found 15 patients (33%) with isolated hyponatremia, 9 patients (20%) with isolated hypochloremia, 12 patients (27%) with combined hypochloremia and hyponatremia, and normal electrolyte status was evident in the remaining 9 patients (20%).

Regarding clinical data of the recruited patients, significant improvement of respiratory rate was noted in normal and hyponatremic patients on day 3 of diuretic adjustments (p value 0.039 and 0.048 respectively) as well as significant improvement of the ROSS classification in the same groups (p value 0.051 and 0.038) (Table 2).

Table 1 Sex distribution as well as anthropometric measures of the included patients

		Total no. = 45
Age (years)	Median (IQR)	0.75 (0.42–1.2)
	Range	0.21–6
Gender	Male	27 (60.0%)
	Female	18 (40.0%)
Initial weight (kg)	Mean ± SD	5.64 ± 2.74
	Range	2.3–15
Height (cm)	Mean ± SD	69.13 ± 16.66
	Range	40–110
Body mass index	Mean ± SD	13.39 ± 4.21
	Range	6.9–24
Duration of furosemide therapy (months)	Median (IQR)	9.5 (6–12)
	Range	6–66

Initial and follow-up mean serum Na in the hyponatremic group was 132.50 ± 2.07 mEq/L and 134.00 ± 1.76 mEq/L respectively. Mean initial and follow up Cl level in the hypochloremic group was 89 ± 5.23 mEq/L and 94.25 ± 6.50 mEq/L respectively. The combined hypochloremic hyponatremic group showed initial levels of serum Na of 131.88 ± 2.17 mEq/L and initial Cl level of 89.13 ± 26 mEq/l. These values changed to133.75 ± 1.75 mEq/L and 90 ± 9.15 mEq/L respectively on day 3 of therapy (Table 3).

Assessment of urinary parameters in the 4 groups is shown in Table 4 with no significant differences between them initially. On day 3, patients with combined hyponatremia and hypochloremia had the lowest Na/K ratio with a median of 1.53, followed by hypochloremic patients who had a median Na/K ratio of 1.95, in comparison to hyponatremic patients who had a median ratio of 3. All patients have shown a considerable increase in their UOP but on calculating net fluid output and relating it to the dose of diuretics given, patients with combined hyponatremia and hypochloremia had the lowest net fluid output/40 mg furosemide with a mean of 562.55 ± 618.43 ml. Hypochloremic patients had also low fluid output/40 mg furosemide with a mean of 908.33 ± 668.81 ml in comparison to a mean of 1502.10 ± 518.12 ml in hyonatremic patients and a mean of 1508.28 ± 412.79 ml in the normal group (Table 4)

Furthermore, on relating the change in body weight to the furosemide dose given, we found very low change in body weight in the hypochloremic group as well as the hypochloremic hyponatremic group (median of 0.093 mg and 0.005 mg respectively), in contrast to a median change of 0.51 mg and 0.385 mg in the hyponatremic and normal group respectively (Table 5).

Table 2 Clinical data of included patients at baseline and at day 3 after dose adjustment

		Hyponatremia No. = 15	**Hypochloremia No. = 9**	**Both No. = 12**	**Normal No. = 9**
Respiratory rate (per minute)					
Day 1	Mean ± SD	52.88 ± 4.29	52.06 ± 6.13	43.61 ± 6.79	51.21 ± 6.17
	Range	48–60	40–60	30–55	40–60
Day 3	Mean ± SD	43.19 ± 5.42	52.17 ± 3.71	40.25 ± 8.47	41.21 ± 9.54
	Range	30–52	48–60	25–55	25–55
p value		0.048	0.956	0.239	0.039
Systolic blood pressure (mmHg)					
Day 1	Mean ± SD	81.75 ± 4.49	81.67 ± 5.69	86 ± 5.77	83.79 ± 6.34
	Range	75-90	70-90	80-100	70-90
Day 3	Mean ± SD	86.75 ± 4.36	84.25 ± 4.85	88.17 ± 6.13	87 ± 7.48
	Range	80–90	75–90	80–100	80–100
p value		0.910	0.208	0.334	0.314
Diastolic blood pressure (mmHg)					
Day 1	Mean ± SD	48.13 ± 2.85	49.06 ± 4.89	51.94 ± 4.25	50.64 ± 5.92
	Range	45–55	40–60	45–60	40–60
Day 3	Mean ± SD	51.25 ± 3.42	49.67 ± 4.42	52.5 ± 4.52	53.21 ± 5.04
	Range	45–60	45–60	45–60	45–60
p value		0.217	0.730	0.735	0.141
Capillary refilling time (seconds)					
Day 1	2	5 (33.3%)[1]	6 (66.6%)	6 (50%)	6 (66.7%)
	3	10 (66.7%)	3 (33.3%)	6 (50%)	3 (33.3%)
	4	0%	0%	0%	0%
Day 3	2	7 (46.7%)	5 (55.5%)	5 (41.7%)	5 (55.5%)
	3	8 (53.3%)	4 (44.4%)	7 (58.3%)	4(44.4%)
	4	0%	0%	0%	0%
p value		0.105	0.232	0.279	0.070
Ross classification					
Day 1	I	0%	0%	0%	0%
	II	0%	0%	6 (50.0%)	0%
	III	5 (33.3%)	5 (55.5%)	3(25%)	6 (66.7%)
	IV	10 (66.7%)	4 (44.4%)	3 (25%)	3 (33.3%)
Day 3	I	6(40%)	0%	0%	2 (22.2%)
	II	6(40%)	0%	5 (42.7%)	3 (33.3%)
	III	3(20%)	6 (66.6%)	4 (33.3%)	4 (44.4%)
	IV	0%	3 (33.3%)	3(25%)	0%
p value		0.038	0.063	0.794	0.051
Cardiothoracic ratio					
Day 1	Mean ± SD	0.56 ± 0.03	0.55 ± 0.04	0.53 ± 0.03	0.55 ± 0.04
	Range	0.5–0.6	0.5–0.6	0.49–0.58	0.5–0.6
Day 3	Mean ± SD	0.53 ± 0.03	0.56 ± 0.03	0.54 ± 0.02	0.53 ± 0.03
	Range	0.5–0.58	0.52–0.6	0.5–0.58	0.49–0.58
p value		0.476	0.193	0.198	0.574
Lung congestion					
Day 1	Mild	3 (20%)	2 (22.2%)	0%	2 (22.2%)
	Moderate	7 (46.7%)	6 (66.7%)	9 (77.8%)	5 (55.6%)
	Severe	5 (33.3%)	1 (11.1%)	3 (22.2%)	2(22.2%)
Day 3	Mild	11 (73[2].3%)	2 (22.2%)	0%	6(66.7%)
	Moderate	4 (26.7%)	5 (55.5%)	8 (66.7%)	3 (33.3%)
	Severe	0%	2 (22.2%)	4 (33.3%)	0%
p value		0.544	0.262	0.500	0.258

[1] Day 1= initial assessment on presentation, [2]Day 3= assessment three days after diuretic dose adjustment

Discussion

Despite the widespread use of diuretics in children, there has been paucity of prospective studies about the frequency and degree of serum electrolyte abnormalities after diuretic use in this population. The main aim of our study was to highlight the incidence of serum chloride and serum sodium derangements in patients on prolonged furosemide therapy as well as the possible effects of these derangements on their diuretic response.

Out of our studied population, 20% of patients had isolated hypochloremia, 33% with isolated hyponatremia and 27% had combined hyonatremia and hypochloremia. Numerous reports documented the occurrence of diuretic-induced hyponatremia in adult patients especially elderly females [13]. In their study,

Table 3 Blood chemistry of the included patients

		Hyponatremia No. = 15	Hypochloremia No. = 9	Both No. = 12	Normal No. = 9	*P* value	Sig.
Day 1							
Serum Na (mEq/dL)	Mean ± SD	132.50 ± 2.07	136.75 ± 1.71	131.88 ± 2.17	139.00 ± 3.34	0.000	HS
	Range	128–135	135–139	129–135	135–144		
Serum K (mEq/dL)	Mean ± SD	4.55 ± 0.74	4.35 ± 0.72	4.96 ± 0.51	4.23 ± 1.11	0.326	NS
	Range	3.3–5.5	3.4–5	4.3–6	2.4–5.9		
Serum Cl (mEq/dL)	Mean ± SD	103.50 ± 4.35	89 ± 5.23	89.13 ± 26	101.63 ± 4.57	0.000	HS
	Range	97–109	84–94	85–95	98–109		
Day 3							
Serum Na (mEq/dL)	Mean ± SD	134.00 ± 1.76	135.25 ± 0.50	133.75 ± 1.75	136.50 ± 1.60	0.007	HS
	Range	131–138	135–136	131–136	134–138		
Serum K (mEq/dL)	Mean ± SD	4.48 ± 0.49	4.10 ± 0.73	4.65 ± 0.50	4.13 ± 0.92	0.347	NS
	Range	3.8–5.1	3.5–5	4.3–5.7	3.2–5.5		
Serum Cl (mEq/dL)	Mean ± SD	101.40 ± 7.89	94.25 ± 6.50	90 ± 9.15	97.13 ± 4.42	0.025	S
	Range	86–110	85–100	72–100	91–104		

Cl serum chloride, *K* serum potassium, *Na* serum sodium

Table 4 Urinary parameters of the included patients

		Hyponatremia No. = 15	Hypochloremia No. = 9	Both No. = 12	Normal No. = 9	*P* value	Sig.
Day 1							
Urine Na/k	Median (IQR)	1.69 (0.83–2.33)	2.43 (2.77–11.65)	1.65 (0.92–5.89)	1.29 (0.89–2.11)	0.235	NS
	Range	0.28–4.7	1.18–16.8	0.23–10.3	0.3–2.42		
UOP (ml/kg/h)	Mean ± SD	2.08 ± 0.39	1.88 ± 0.25	1.91 ± 0.56	2.56 ± 0.62	0.055	NS
	Range	1.5–3	1.5–2	1–3	1.5–3		
Net fluid output/40 mg furosemide	Mean ± SD	1401.60 ± 681.09	852.00 ± 126.24	1385.25 ± 770.11	1760 ± 815.84	0.243	NS
	Range	640–2880	720–960	768–2880	640–2880		
Day 3							
Urine Na/k	Median (IQR)	3 (2–3.1)	1.95 (1.69–2.5)	1.53 (1.46–1.92)	2.49 (1.6–3)	0.022	S
	Range	1.49–4.6	1.48–3	1–2.99	1.54–3		
UOP (ml/kg/h)	Mean ± SD	4.17 ± 0.68	5.08 ± 1.26	4.80 ± 1.12	4.58 ± 0.60	0.294	NS
	Range	2.5–5	3.5–6.5	3.4–6	3.5–5		
Netfluid output/40 mg furosemide	Mean ± SD	1502.10 ± 518.12	908.33 ± 668.81	562.55 ± 618.43	1808.28 ± 412.79	0.003	HS
	Range	500–2560	320–1760	125.2–2000	1000–2176		

UOP Urine output

Table 5 Parameters of diuretic response in the different patients groups

		Hyponatremia No. = 15	Hypochloremia No. = 9	Both No. = 12	Normal No. = 9	*P* value	Sig.
Day 1 weight	Mean ± SD	4.33 ± 1.57	8.63 ± 5.12	5.69 ± 2.19	5.75 ± 2.10	0.061	NS
	Range	2.3–7	3–15	4–10	4–10		
Day 3 weight	Mean ± SD	3.64 ± 1.51	8.15 ± 5.16	5.26 ± 2.12	5.00 ± 2.13	0.058	NS
	Range	2–6.3	2.3–14.5	3.5–9.5	3.5–9.6		
Change in body weight	Mean ± SD	0.69 ± 0.26	0.48 ± 0.21	0.43 ± 0.14	0.75 ± 0.22	0.038	S
	Range	0.2–1	0.2–0.7	0.2–0.5	0.2–1		
Cumulative furosemide dose (mg)	Median (IQR)	28.9 (17.3–38.5)	97.75 (61.06–120.85)	88 (65.3–99.6)	38.95 (29–47.73)	0.000	HS
	Range	11.9–57	45.12–123.2	53.6–106.4	23.4–62		
Change in body weight/total diuretic dose	Median (IQR)	0.51 (0.19–0.69)	0.093 (0.008–0.215)	0.005 (0.004–0.108)	0.385 (0.135–0.515)	0.002	HS
	Range	0.027–1	0.001–0.26	0.003–0.25	0.018–0.63		

Ogawa et al. studied 126 infants on diuretic therapy; serum sodium concentration < 134 mEq/l was found in 14.3% of patients [14]. Although similar mechanisms that lower sodium may also lower chloride levels, lower chloride levels may represent a broader homeostatic imbalance. Chloride plays a role in acid–base homeostasis, contributes to maintenance of urine and plasma electroneutrality, and may even effect neurohormonal activation. Extensive literature from murine models has demonstrated that chloride (and not sodium) in the renal tubular fluid suppresses plasma renin activity after resorption in the thick ascending limb and by direct action on the macular densa. This mechanism can be suppressed with chronic loop diuretic use which blocks chloride resorption in the thick ascending limb and, over time, leads to excessive chloride loss, translating into hypochloremia [15].

All patients included in our study were those on prolonged furosemide therapy more than 6 months due to chronic congestive state and who required an increase in their diuretic dose to control their symptoms.

The term 'diuretic resistance' remains inadequately defined despite its increasing frequency. It can be defined as failure to reduce extracellular fluid despite using adequate dose of diuretics [9]. While clinical characteristics of patients with diuretic resistance have been identified, a reliable prospective measure identifying those who have suboptimal diuretic and natriuretic responsiveness has not been extensively studied [16]. Researches had focused on defining diuretic and natriuretic responsiveness based on change in body weight or urine output relative to the dose of furosemide administered [4].

In our study, we studied diuretic response based on changes in urinary Na/K ratio, Net fluid output and change in body weight/40 mg furosemide.

In his study, EL Basel et al. [17] tested the correlation between spot urinary Na/k ratio and 24-h urinary sodium. They found a significant correlation between the two with sensitivity 75% and specificity 91.6%. They also showed that spot urinary Na/K ratio was significantly lower in patients with diuretic resistance versus the sensitive group ($p < 0.05$). Similar results were obtained by other authors as well [18, 19]. In our study, we compared urinary Na/K ratio on day 3 to that on day 1. We considered increased urinary Na/K ratio a reflection of natriuresis and good diuretic response. Out of the four studied groups, patients with hypochloremia (either isolated or combined with hyponatremia) showed lowest urinary Na/K ratio on day 3 with a median of 1.95 in the former group and 1.53 in the latter group. On the other hand, hyponatremic patients had a higher median urinary Na/K ratio of 3, which was very close to that of the normal patients.

As for net fluid output, all candidates showed an increase in their urine output on day 3 of therapy. However, on calculating net fluid output and relating it to the dose of furosemide given we have found that hyponatremic hypochloremic patients had the lowest fluid output/40 mg furosemide, followed by the isolated hypochloremic group. It is worth mentioning that patients with hyponatremia had a near normal fluid output/40 mg furosemide denoting a good diuretic response.

Similar results were obtained when considering changes in body weight in relation to dose of furosemide given. Although all patients showed a decrease in their weight on day 3 of therapy, yet hypochloremic hyponatremic patients had the lowest change in body weight followed by the hypochloremic group. Median decrease in body weight in these groups was much less than that observed in the hyponatremic group or the normal patients.

All the three parameters pointed to an element of diuretic resistance most prominent in the hyponatremic hypochloremic and the isolated hypochloremia group,

despite the fact that isolated hyponatremia per se was not associated with diuretic resistance at all.

The finding of diuretic resistance in hypochloremic patients comes in agreement with the PROTECT study in which diuretic response was defined as weight change on day 4 per 40 mg of intravenous furosemide (or equivalent doses) administered from baseline to day 3. There was less weight change, higher diuretic doses, smaller percentage change in BNP levels from baseline, and more frequent requirement for adjuvant thiazide diuretics or inotropes during hospitalization in patients with hypochloremia (all $P < 0.01$). In addition, patients with low chloride had a significantly lower rate of improvement in intravascular volume, as indicated by a 20% absolute difference in hemoconcentration across quintiles of chloride. Chloride remained significantly associated with diuretic response, even after correction for sodium and bicarbonate levels in addition to potential baseline and in-hospital confounders ($P < 0.001$). Other studies have shown similar results as well [20, 21]. Hanberg et al. [21] reported that serum chloride was significantly associated with diuretic efficiency whereas serum sodium was not.

On the other hand, Paul et al. [22] reported that compared with normonatremic patients, those with hyponatremia required higher doses of intravenous loop diuretic, had less early but ultimately similar weight loss, and despite the higher diuretic doses, they had less relief of dyspnea.

This is contradictory to our results which pointed out to the fact that although isolated hyponatremia does not affect the diuretic response except if associated with concomitant hypochloremia.

Actually, the incidence of diuretic resistance in cases with combined hyponatremia and hypochloremia has not been extensively studied, except for the study of Cuthbert et al. [23]. who stated that hypochloremia, regardless of sodium levels, was associated with higher risk of mortality or heart failure hospitalization than isolated hyponatremia and serum sodium was not associated with adverse outcome after adjustment for other variables, including chloride.

Conclusion

Abnormalities in serum Cl and Na are quite common in paediatric patients on prolonged furosemide therapy. The occurrence of such abnormalities may adversely affect diuretic response in these patients. Unlike isolated hyponatremia, isolated hypochloremia can result in significant diuretic resistance. Combined hypochloremia and hyponatremia is associated with the worst diuretic response when compared to isolated hypochloremia or hyponatremia.

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Authors' contributions
N.S. gave substantial contributions to the conception and the design of the work, as well as to the interpretation of data and revising it. A.K. gave substantial contributions to the conception and design of the work as well as its revision. M.S. made contributions to data acquisition and analysis. E.E. contributed to the data acquisition and analysis as well as creation of the software and statistical analysis. All authors have approved the submitted version of the study and agreed to be personally accountable for their contributions.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All participants' parents or legal guardians gave their informed consent after approval of the ethical Committee of the Faculty of Medicine of Ain Shams University. The work complies with the principles of the Declaration of Helsinki in 1964.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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