RESEARCH PAPER

Free Water Excess is Not the Main Cause for Hyponatremia in Critically Ill Children Receiving Conventional Maintenance Fluids

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Objective: To examine occurrence of hyponatremia in critically ill children receiving conventional maintenance fluids (0.18% saline in 5% dextrose) and its relationship with electrolyte free water (EFW), sodium intake and natriuresis.

Design: Prospective observational study.

Setting: Pediatric Intensive Care Unit of a tertiary care teaching hospital.

Subjects: Thirty eight patients, 3 months-12 years, consecutively admitted to PICU over 30 days. Main outcome measure was occurrence of hyponatremia (serum sodium ≤130 mEq/L). Serum and urinary sodium, and osmolality were measured, and type and volume of intravenous fluids and total urine output were recorded 12 hourly. Daily intake of sodium and EFW, urinary sodium excretion and net balance of fluid and sodium were estimated from above. Data of hyponatremic and non-hyponatremic patients was compared using ANOVA, Mann-Whitney U, and Chi-square tests.

Results: Fourteen episodes of hyponatremia were recorded in 12 patients over 397 patient days (3.5 episodes/100 patient days). Their mean (SD) serum sodium dropped from 139 (9.3) at admission to 128 (1.0) mEq/L, over a median interval of 3.5 days (range 1-15 days). Net fluid and sodium balance in hyponatremic patients did not differ significantly from non-hyponatremic patients. Within the hyponatremic group, sodium intake, urinary sodium and sodium balance were similar before and after the occurrence of hyponatremia, while total fluid (P=0.009) and EFW intake (P=0.001) were lower in the days preceding hyponatremia.

Conclusions: Fluid and sodium balance, magnitude of natriuresis and EFW intake alone did not explain occurrence of hyponatremia in critically ill children; contribution of other mechanisms needs to be studied.

Keywords: *Electrolyte free water, Fluid therapy, Hyponatremia, Maintenance fluids, Sodium balance.*

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Hyponatremia is the most common electrolyte disorder in hospitalized critically ill patients(1,2). This could result from a deficit of sodium or a surplus of water(3). Most often it has been attributed to free water excess resulting from impaired free water excretion that is caused by an inappropriate release of antidiuretic hormone in response to various non-osmotic stimuli(4). Use of conventional "hypotonic" maintenance fluid (0.18% saline in 5% dextrose) has been alleged to aggravate this free water excess in sick children in whom the excretion of hypotonic urine is impaired(5,6).

Intracellular fluid (ICF) volume is inversely related to the serum sodium; therefore, hyponatremia may aggravate the risk of cerebral edema and herniation(3,7,8). The reported morbidity and

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mortality associated with hospital-acquired hyponatremia have given momentum to calls for increasing the tonicity of the parenteral maintenance solution(5,6,9). Some authors on the contrary feel that simple restriction of fluids rather than isotonic saline would tackle the problem better, by improving the secondary desalination that results from over expansion of the intravascular space(10,11). The debate on the issue continues(10-12).

With this background, we have examined the relationship of hyponatremia with free water intake, sodium intake and natriuresis in critically ill children receiving conventional maintenance fluids (0.18% saline in 5% dextrose). Our hypothesis was that occurrence of hyponatremia is not fully explained by electrolyte free water (EFW) intake, that occurs with conventional maintenance fluids and natriuresis, that occurs in sick children. In our previous studies, hyponatremia was seen in sick children attending pediatric emergency service even before they had received intravenous fluids(13) and it got corrected in patients with pneumonia(14) and meningitis(15) while receiving 0.18% saline in 5% dextrose as maintenance fluids, with improvement in primary disease.

METHODS

This was a prospective observational study conducted in the Pediatric Intensive Care Unit (PICU) of a multi-specialty teaching and regional referral hospital in North India from mid March 2004 to mid April 2004, after approval from the Institute's Ethics Committee. All patients admitted to the PICU during this period were enrolled consecutively into the study except those who had a PICU stay <24 hours.

Demographic details, weight, diagnosis, PRISM scores and indication for PICU admission were recorded. Nutritional status was assessed as percentage weight for age, using NCHS standards and IAP Classification(16). Serum sodium (Dimension Clinical Chemistry Analyzer, Dade Behring, USA) and osmolality (Model 3300, Advanced Instuments, Norwood, USA) were measured 12 hourly. Urine was collected every 12 hours and sodium concentration estimated from an aliquot from total collection. Sodium levels were measured using ion selective electrodes.

Volume and type of intravenous and oral fluids given to patients and total urine output were recorded. Intake of fluids (mL/kg/day), sodium (mEq/kg/day) and electrolyte free water (EFW) (mL/kg/day), urine output (mL/kg/day), and urinary sodium excretion (mEq/kg/day) were derived from above data. Net daily balance of fluid and sodium were estimated from 24-hour fluid and sodium intake, urine output and urinary sodium excretion. The EFW input was calculated using the tonicity and the volume of the fluid infused(12). For example, for every litre of 0.18% saline in 5% dextrose that was infused, only one-fifth *i.e*, 200 mL is isotonic to plasma and the rest 800 mL is EFW.

Data analysis: Any record of serum sodium ≤130 mEq/L was counted as one episode of hyponatremia. If more than one consecutive serum sodium levels were ≤130 mEq/L, before it got corrected, it was counted as one episode. Hyponatremia was corrected as per standard protocol if patient was symptomatic or if the level was <125 mEq/L(17). The influence of EFW intake on serum sodium was analyzed using the initial measured sodium and total body water (which was estimated as 60% of body weight)(6). To examine relationship of hyponatremia with free-water intake, sodium intake and natriuresis, the data of hyponatremic patients on all the days preceding the episode of hyponatremia was compared with the data of all the days following the occurrence of hyponatremia. Additionally, the data of hyponatremic patients on all the days preceding hyponatremia was also compared with that of the normonatremic children (serum sodium >130 mEq/L). Descriptive statistics (frequency, median, mean and SD) were used for data presentation. For comparisons across the three groups, ANOVA was used for parametric data and Mann Whitney- U test for non-parametric data. Categorical data were compared using the Chi Square test.

RESULTS

Thirty-eight patients, aged 2 months to 13 years, with a median PRISM score of 13 (range 4-20) were included in the study. They comprised 397 patient-

days. 29 children had malnutrition (weight for age <80% of expected); 20% (6/29) of them had severe malnutrition (weight for age <60% of expected).

Fourteen episodes (3.5 episodes/100 patient days) of hyponatremia were recorded. One patient was hyponatremic at admission to PICU, while 13 episodes occurred in 11 patients during the ICU stay; 2 patients had 2 episodes each. The mean (SD) serum sodium in these patients had dropped from 139 (9.6) mEql/L (range 131-154 mEq/L) to 128 (1.0) mEq/L (range 127-129 mEq/L). The median time from admission to occurrence of hyponatremia was 3.5 days (range 1-15 days). The median serum and urine osmolality at the time of detection of hyponatremia were 276 (260-329) mOsm/kg and 340 (180-649) mOsm/kg, respectively. The salient characteristics of patients who had hyponatremia compared with those having normal serum sodium are depicted in ***Table* I**. Diagnosis of myocarditis and use of diuretics were significantly more frequent in hyponatremic patients. The proportion of malnourished patients in both the groups were similar (10 out of 12 vs 19 out of 26, *P*=0.9).

Relationship of EFW intake and fall of serum sodium

The median (5th-95th centile) EFW intake among the hyponatremic patients before occurrence of hyponatremia was 70.7 (21.1-105.0) mL/kg/day. The correlation between EFW intake and the fall in serum sodium was not significant (Pearson's correlation r = –0.574; *P*=0.083). Only 4 patients had received an EFW volume that could explain fall in their serum sodium **(*Fig.* 1)**. The hyponatremic patients (before and after occurrence of hyponatremia) and the non-hyponatremic patients had similar fluid and sodium balance and sodium excretion **(*Table* II)**. Within the hyponatremic group, in the days preceding hyponatremia compared to the days following hyponatremia, the median (5th-95th centile) sodium intake and excretion were not significantly different but total fluids and EFW intake and urine output mL/kg/day was significantly lower **(*Table* II).** Total fluid intake and EFW intake in pre-hyponatremic phase was also significantly lower than that in patients without hyponatremia.

TABLE I CHARACTERISTICS OF PATIENTS WITH HYPONATREMIA AND NORMONATREMIA

Characteristics	Hyponatremia (*n*=12)	Normonatremia (*n*=26)	*P* value
Age (years)	5.5 (3.6)[a]	4.2 (4.0)[a]	0.41*
Male:Female	1.4:1	2.3:1	
PRISM score	13.5 (4-20)[b]	9 (5-20)[b]	0.46[†]
Weight for age, % of expected	75.2 (12.3)[a]	78.7 (14.9)[a]	0.45*
Mechanical ventilation, *n* (%)	6 (50)	13 (50)	0.72
Use of diuretics, *n* (%)	4 (33)	1 (4)	0.047
Diagnosis, *n* (%)			
Pneumonia	4 (33.3)	2 (7.6)	0.12
Myocarditis with cardiogenic shock	4 (33.3)	–	0.01
Pyogenic meningitis	3 (25)	3 (11.5)	0.29
Congenital heart disease	–	4 (15.4)	
Pericardial effusion	–	1 (3.8)	
Others	1 (8.3)	14[c] (53.8)	
Serum osmolality, mOsm/ Kg	276 (260-329)[b]	280 (262-310)[b]	0.17[†]

** P by Students' t test, [†]P by Mann Whitney U test; [a]mean (SD), [b]median (range); [c]includes acute gastroenteritis (n=3), acute leukemia with febrile neutropenia (n=2), acute laryngotracheobronchitis (n=2) and nephrotic syndrome with septic shock (n=2) acute leukemia with acute gastroenteritis, tetanus, snake envenomation, diphtheria and acute liver failure (n=1 each).*

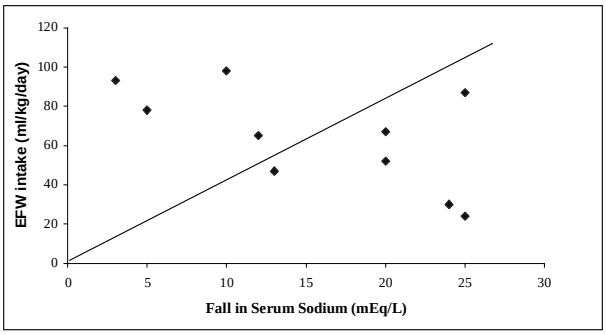

FIG. 1 *Relationship between electrolyte free water (EFW) intake and fall in serum sodium. The line indicates expected fall in serum sodium for the given EFW intake. Each dot represents data of one patient and shows observed fall in serum sodium with respect to their EFW intake. The correlation between EFW intake and the fall in serum sodium was not significant (Pearson's correlation r=–0.574; P=0.083).*

Although the use of diuretics were more frequent in hyponatremic patients, urine output, and sodium and fluid balance was not significantly different in the patients who received diuretics and who did not. In fact, total fluid, EFW intake and sodium excretion were lower in patients who received diuretics **(*Table* III).** Possibly the patients in diuretic group were those who needed an improvement in their urine output because of their underlying conditions and diuretics were used to normalize urine output.

There were 8 deaths in the study population; 2 in hyponatremic and 6 in those having serum sodium >130 mEq/L group (*P*=0.65). None of the deaths were directly attributable to hyponatremia.

DISCUSSION

The incidence of hyponatremia in study population was 3.5 episodes/100 patient days. The difference in incidence compared to that reported previously by other authors is probably related to the lower cut off values taken for definition of hyponatremia (≤130 mEq/L in our study versus ≤136 mEq/L in other studies)(5,6)**.** Cut off of ≤130 mEq/L was used by us because in a previous study we found it to be associated with significant increase in mortality in sick children attending pediatric emergencies(13).

TABLE II FLUID AND SODIUM BALANCE IN PATIENTS WITH HYPONATREMIA, BEFORE AND AFTER OCCURRENCE OF HYPONATREMIA, COMPARED TO PATIENTS WITHOUT HYPONATREMIA

	Preceding hyponatremia (A)	Following hyponatremia (B)	No hyponatremia (C)	*P* value
Urine output (mL/kg/day)	48.4 (15.6–91.7)	70.1 (31.3–128.8)	62.8 (54.9–153)	0.005 A vs B =0.002
Total fluid intake (mL/kg/day)	91.0 (35–130)	106 (57–151)	98.6 (55.4–151)	0.009 A vs B =0.016 A vs C =0.007
Fluid balance (mL/kg/day)	32.5 (1.2–85.3)	40 (5.0–90.0)	44.7 (3.4–96)	0.076
Electrolyte free water (mL/kg/day)	70.7 (21.1–105.0)	91.7 (52.3–135.2)	83.2 (42.4–108.7)	<0.0001 A vs B =0.002 A vs C =0.000 B vs C =0.031
Sodium intake (mEq/kg/day)	2.4 (0.2–11.9)	1.6 (0.2–9.1)	2.3 (0.2–7.4)	0.028 B vs C =0.017
Urinary sodium (mEq/kg/day)	2.8 (1.5–20.1)	5.3 (1.3–21)	5.8 (1.0–15.4)	0.4
Sodium balance (mEq/kg/day)	1.2 (–13.2–11.7)	0.20 (–15.2–4.9)	0.45 (–13.2–7.9)	0.3

Values show median (5th–95th centile).

We found that though the hyponatremic children were hypo-osmolar with a net positive fluid balance, the magnitude of the positive fluid balance, sodium balance and natriuresis in the days preceding hyponatremia in these patients was similar to that of post hyponatremic phase and those having serum sodium >130 mEq/L group. Over expansion of intravascular space and dilutional hyponatremia usually results from either an increased EFW intake or an impaired water excretion(5). In our patients, the magnitude of EFW intake alone could not explain the fall in serum sodium in all the patients. In fact the EFW intake and fluid balance was lower in the hyponatremic group compared to the normonatremic group. Our observations are in contrast to the findings reported by Hoorn, *et al.*(6) and Moritz, *et al.*(9). The former, in their retrospective study on hospital-acquired hyponatremia, demonstrated that intake of EFW in the form of hypotonic infusions was a major cause for fall in serum sodium. These authors felt that though SIADH was a part and parcel of critical illness, hyponatremia occurred only in the setting of an associated increased water intake(6). This hypothesis was supported by the latter group, which demonstrated that administration of hypotonic fluids was the main contributor to hospital-acquired hyponatremia(9).

These reports had challenged the conventional practice of use of hypotonic maintenance fluids and suggested that these be replaced by isotonic saline(6,9,18). This, however, could not be accepted universally because of contrasting concerns. First concern is the ongoing natriuresis, which may negate the effect of this intervention(19,20). Giving intravenous isotonic saline solutions to acutely ill children leads to more sodium excretion than water(6,11,19). The other is the risk of sodium overload and hypernatremia in presence of isotonic fluids in children due to their minimal excretory capacity of sodium(21,22).

Impaired excretion of free water, as a result of SIADH secondary to various osmotic and non-osmotic stimuli is a common event in critically ill children(23). Excessive ADH production may cause secondary increase in net urinary sodium loss (desalination), which is attributed to suppression of aldosterone caused by SIADH mediated water retention and over expansion of the intravascular space(24). Hence, hyponatremia in the setting of SIADH is primarily dilutional while secondary natriuresis sustains the hyponatremia. Though the findings in our hyponatremic group could be explained on the basis of SIADH, this does not explain why those having serum sodium >130 mEq/L group with similar fluid and sodium balance did not become hyponatremic. This, therefore, points to contribution from an alternative mechanism, other than water retention, increased water input or excessive natriuresis.

Hyponatremia could occur due to redistribution of sodium without an actual loss. An intracellular shift of sodium chloride and water has been shown in an experimental model of early septic shock(25). A combination of intracellular shift of sodium and dilution of extracellular spaces due to water

TABLE III FLUID AND SODIUM BALANCE OF PATIENTS WITH HYPONATREMIA WITH RESPECT TO USE OF DIURETICS

	Diuretics used	Diuretics not used	*P* value
Intake (mL/kg/day)	95.0 (31-199)	105.0 (38-183)	0.05
Urine output (mL/kg/day)	54.3 (15.4-166)	60.9 (14.5-112.5)	0.1
Fluid balance (mL/kg/day)	31.6 (–20.5-179.0)	41.4 (3.2-316)	0.2
Electrolyte free water intake (mL/kg/day)	66.8 (13.9-176)	89.7 (24.2-135.2)	0.008
Sodium intake (mEq/kg/day)	2.0 (0.23-16)	1.7 (0.08-14.4)	0.08
Sodium excretion (mEq/kg/day)	3.5 (0.57-24.2)	7.2 (1.9-20.1)	0.005*
Sodium balance (mEq/kg/day)	0.90 (–33.9-11.7)	0.12 (–16.6-14.4)	0.1

*Values represent median (5th -95th Centile); *Mann-Whitney U test.*

WHAT IS ALREADY KNOWN?

- Hyponatremia in hospitalized critically ill patients is attributed to free water excess resulting from impaired free water excretion and use of conventional maintenance fluids.

WHAT THIS STUDY ADDS?

- It does not support the contention that use of conventional maintenance fluid (0.18% saline in 5% dextrose) is the main cause of hyponatremia in such patients.

retention in this model resulted in hyponatremia and hypoosmolarity(26). Increase in RBC sodium coinciding with hyponatremia in sick septicemic children further substantiates this mechanism of translocation(27).'Sick cell hypothesis' may be other mechanism for hyponatremia; in critically ill patients; intracellular solutes may leak out of the cell due to increased membrane permeability causing redistribution hyponatremia, with an increased osmolar gap(28,29). Indeed, 'osmolar gap' hyponatremia has been postulated as a mechanism in more than 50% of hyponatremic episodes in adult ICU patients(28,29). Since we did not find enough evidence to suggest significant EFW excess or natriuresis to explain the fall in sodium, we postulate that translocation and redistribution could have been a possible mechanism in our patients. This may also possibly explain the normal or high osmolality in some of our patients in the absence of hyperglycemia or mannitol therapy. This argument is further supported by our previous observations on pneumonia and meningitis patients(14,15); hyponatremia that was present at admission in these patients corrected itself over 3-5 days concomitant with recovery from illness while the patients were receiving 0.18% saline in 5% dextrose as maintenance fluid.

There are some limitations in this study. The study sample was small, which may have limited the significance of differences in hyponatremic and non-hyponatremic group with respect to EFW intake and sodium excretion. The cut off value of hyponatremia was ≤130 mEq/L, in contrast to ≤135 mmol/L, which might have influenced the incidence of hyponatremia in our study.

To conclude, our findings do not support the contention that use of conventional hypotonic maintenance fluids is the main cause of hyponatremia in critically ill children. Whether an alternative mechanism such as translocation and/or redistribution of sodium contributes to hyponatremia in sick children needs further investigation.

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