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ORIGINAL PAPER

Normal saline is a safe initial rehydration fluid in children with diarrhea-related hypernatremia

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Abstract To demonstrate safety and efficacy of using normal saline (NS) for initial volume expansion (IVE) and rehydration in children with diarrhea-related hypernatremic dehydration (DR-HD), forty eight patients with DR-HD were retrospectively studied. NS was used as needed for IVE and for initial rehydration. Fluid deficit was given over 48 h. Median Na^+ level on admission was 162.9 mEq/L (IQR 160.8–165.8). The median average hourly drop at 6 and 24 h was 0.53 mEq/L/h (0.48–0.59) and 0.52 mEq/L/h (0.47–0.57), respectively. Compared to children not needing IVE, receiving ≥40 ml/kg IVE was associated with a higher average hourly drop of Na^+ at 6 h (0.51 vs. 0.58 mEq/L/h, p=0.013) but not at 24 h (p=0.663). The three patients (6.3%) with seizures had a higher average hourly drop of Na^+ at 6 and 24 h (p=0.084 and 0.021, respectively). Mortality (4/48, 8.3%) was not related to Na^+ on admission or to its average hourly drop at 6 or 24 h. Children receiving ≥40 ml/kg IVE were more likely to die (OR 3.3; CI, 1.5–7.2). *Conclusion*: In children with DR-HD, NS is a safe rehydration fluid with a satisfactory rate of Na^+ drop and relatively low incidence of morbidity and mortality. Judicious use of IVE should be exerted and closer monitoring should be guaranteed for children requiring large volumes for IVE and for those showing rapid initial drop of serum Na^+ to avoid neurological complications and poor outcome.

Keywords Hypernatremic dehydration · Normal saline · Rehydration fluids · Diarrhea · Gastroenteritis

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Introduction

Diarrhea-related hypernatremic dehydration (DR-HD) is a serious condition which carries the risk of central nervous system injury both related to illness severity and treatment-related complications. In patients with DR-HD, dehydration results from a child having negative water balance with water loss exceeding any loss of salt [3, 8]. Despite high serum sodium levels, the total body sodium in these patients is depleted [14].

Hypernatremia in children with diarrhea should be suspected in the presence of jitteriness, exaggerated muscle tone and reflexes, myoclonus, asterixis, chorea, disturbed level of consciousness, or seizures. Complications of the condition include intracranial hemorrhage, cerebral edema, cerebral infarctions, and rhabdomyolysis. Hyperglycemia is a common finding in children with hypernatremia. The movement of water from the intracellular space to the extracellular space expands the intravascular volume. Thus, children with DR-HD often present late with less tachycardia and preserved urine output. Unfortunately, the milder manifestations often lead to children with DR-HD presenting late to health care facilities [7, 13, 15].

Low osmolarity oral rehydration solution remains a safe and appropriate solution to correct dehydration and electrolyte abnormalities in children tolerating oral fluid therapy even those with suspected or proven hypernatremia.

Nasogastric route can be considered in children who are unable to drink and those persistently vomiting [9, 15].

Generally speaking, intravenous fluid therapy of children with dehydration comprises three components; initial volume expansion (IVE) via giving fluid bolus(es) to restore the intravascular volume, fluid deficit therapy to correct dehydration and to replace fluids and electrolytes already lost on presentation, and lastly maintenance fluid therapy to meet physiological fluid requirements during the rehydration phase. Replacement of ongoing losses is another component that needs to be considered when applicable. There is no, however, clear consensus on which fluid to use for rehydration of children with DR-HD requiring intravenous fluid therapy.

Many guidelines for management of diarrhea point to the importance of recognizing hypernatremia, yet do not give comprehensive details on the management of the condition [2, 19]. The use of fluid bolus(es) for IVE in children with hypernatremic dehydration is referred to in some guidelines [6, 7, 17] and not in others [15]. Some of those advocating fluid boluses for IVE recommend 0.9% sodium chloride (normal saline, NS) in preference to lactated ringer solution for IVE [7] while others suggest using either solutions and, in severe hypernatremia, a custom-made solution with a final sodium concentration not more than 15 mEq/L below the initial serum sodium level of the patient [17]. The type of fluid recommended for deficit replacement is less controversial. One important guideline published by the National Institute of Clinical Excellence of the UK recommends the use of an isotonic solution such as NS, or NS in 5% dextrose, for fluid deficit replacement and maintenance [15].

In all cases, the rate of drop of serum sodium in these children remains crucial, with an average drop of 0.5 mEq/L/h quoted as the maximum safe rate of drop. A rapid drop of serum sodium is associated with the development of cerebral edema and seizures [1, 7, 10, 15, 17]. We report our experience of 48 children with DR-HD requiring intravenous fluid therapy and managed with NS for IVE, deficit replacement and maintenance therapy, aiming for a slow reduction of serum sodium levels targeting recommended rate of sodium drop.

Methodology

This retrospective study included 48 patients with moderate to severe DR-HD requiring intravenous fluid therapy. Patients were admitted to the pediatric intensive care unit (PICU) of Mansoura University Children's Hospital, Mansoura, Egypt during the period from March 2005 to March 2010. Cases were eligible for enrollment in the study if they had DR-HD with serum sodium above 150 mEq/L on PICU admission. Patients with elevated serum creatinine and/or blood urea nitrogen on admission were enrolled in the study if they had a fractional excretion of sodium less than 1. Patients with chronic renal failure or those presenting with abnormal kidney functions and a high fractional excretion of sodium (>2) on admission were excluded from the study.

The need, amount, and rate for IVE were decided by the admitting consultant based on degree of dehydration and hemodynamic parameters. One or more rapid fluid boluses (20 ml/kg each) of NS were given for IVE over 20 min each. The amount of deficit therapy was based on the assessment of the degree of dehydration and was administered over 48 h as NS in 5% dextrose. The amount of deficit therapy ranged from 25–50 ml/kg/day and was given by continuous infusion over the 48-h period. Maintenance fluid was given as NS in 5% dextrose at a rate of 4 ml/kg/h for the first 10 kg of body weight and 2 mL/kg/h for second 10 kg and 1 ml/kg/h per additional kilogram above 20 kg of body weight [18]. Ongoing losses were replaced by a separate half NS infusion when indicated. Potassium chloride was added to fluid therapy at a concentration of 20 mEq/L.

Half NS in 5% dextrose was started after 48 h in children who continued to require intravenous fluid therapy at this point of time. Associated electrolyte abnormalities were corrected as appropriate.

Serum sodium levels in milliequivalents per liter were recorded on admission (Na−0) and at 6 and 24 h post-admission. Hourly drop rate of serum sodium level was calculated from admission to 6 and 24 h post-admission and between 6 and 24 h (Δ Na 0–6, Δ Na 0–24, and Δ Na 6–24, respectively). Data collected included age, sex, admission serum potassium level, Glasgow coma score, and the degree of dehydration at presentation assessed according to the criteria adapted by the American Academy of Pediatrics Subcommittee on Acute Gastroenteritis [19]. The need, the amount, and the rate of administering fluid bolus(es) for IVE and the development of seizures during admission to PICU admission were also noted. Research ethics committee approved the protocol of data collection.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 15.0 for Windows). Continuous data were expressed as mean±SD and median [interquartile range (IQR)]. The Mann–Whitney *U* test was used for comparison between groups. Categorical data were analyzed using the Fisher's exact test as appropriate. Statistical significance was defined as a p value <0.05.

Results

The study included 48 patients (26 girls, 54.2% and 22 boys, 45.8%) admitted with DR-HD. The mean age was 21.88 (SD 11.67) months, and the median age was 18.5 (IQR 14–28) months. The mean serum sodium level on admission was 163.8 mEq/L (SD 5.2) and the median was 162.9 mEq/L (IQR 160.8–165.8). Table 1 shows the admission serum sodium level (Na−0) and the hourly rate of drop at 6 and 24 h post-admission in all patients. Classifying patients by the amount of IVE they received, there was a statistically significant greater drop of serum sodium level at 6 h in the subset of patients receiving ≥40 ml/kg of IVE (median drop 0.58 mEq/L/h, IQR 0.53–0.64) when compared to those requiring no IVE (median drop 0.51 mEq/L/h, IQR 0.46–0.54) with p=0.013 (Table 2).

Three patients (6.3%) had seizures during their PICU stay (one of those three patients, referred to as patient 1 in Table 5, succumbed later). On comparing these patients to those who did not develop seizures, there was no difference regarding the serum sodium levels on admission. On the other hand, these patients had a statistically insignificant greater hourly Δ Na 0–6 (p=0.084) and statistically significant hourly Δ Na 0–24 and hourly Δ Na 6–24 with p values of 0.021 and 0.037, respectively (Table 3). Two of these three patients received ≥40 ml/kg and one received 0–20 ml/kg as IVE.

Mortality among the group of patients was 8.3% (four children). One child (patient 1 in Table 5) presented with seizures and subdural and intracerebral bleeding. Two others developed neurological manifestations suggestive of cerebral edema within the first 24 h after admission. Computed tomography (CT) scan of the brain was performed and was suggestive of cerebral edema in these two cases. The fourth patient (patient 3 on Table 5) had a sudden unexplained asystole. None of these children showed signs suggestive of refractory shock or volume overload. Time of death was in day 2 of admission in all cases. Autopsy was not performed in any of the succumbed children. Mortality was not related to patient's age, severity of dehydration, serum sodium level on admission, hourly Δ Na 0–6, or hourly Δ Na 0–24 (Table 4). Patients were more likely to die if they were given 40 ml/kg or more for IVE with an OR of 3.3 (CI=1.5–7.2). The details of the four children who succumbed are shown in Table 5.

Table 1 Serum sodium on admission and the hourly drop rate in children with DR-HD

	Mean±SD	Median (IQR)
Na−0 (mEq/L)	163.8±5.2	162.9 (160.8–165.8)
Hourly Δ Na 0–6 (mEq/L/h)	0.54±0.10	0.53 (0.48–0.59)
Hourly Δ Na 0–24 (mEq/L/h)	0.52±0.08	0.52 (0.47–0.57)
Hourly Δ Na 6–24 (mEq/L/h)	0.52±0.09	0.52 (0.45–0.59)
Serum potassium (mEq/L)	3.58±0.85	3.60 (2.95–4.20)

Na−0 serum Na on admission, *Δ Na 0−6* drop of serum Na from admission to 6 h, *Δ Na 0–24* drop of serum Na from admission to 24 h, *Δ Na 6−24* drop of serum Na from 6 to 24 h post-admission

Discussion

Hypernatremia is a rare yet a serious complication of gastroenteritis. There are no published randomized controlled trials on which fluid to use for initial fluid management. Published guidelines are increasingly advocating the use of NS for initial rehydration of children with DR-HD. Two major points of agreement among all published guidelines are the seriousness of the condition and the need to lower serum sodium slowly with the rate of 0.5 mEq/L/h generally depicted as the safe maximum. Using NS as an initial rehydration fluid in our cohort resulted in a satisfactory rate of drop of serum sodium in the first 24 h, the period most likely to show complications of treatment.

The rapid drop of serum sodium level at the initial phase of rehydration was associated with seizures in three patients, and statistically significant relations were observed with higher hourly Δ Na 0–24 and Δ Na 6–24 with p values of 0.021 and 0.037, respectively (Table 3). Although using ≥40 ml/kg of NS for initial volume resuscitation was associated with a significant drop of serum sodium level at 6 h when compared to those not receiving IVE (p=0.013), and a tendency to a higher drop rate at the same point of time when compared to patients receiving 20 ml/kg as IVE (p=0.085) as shown on Table 2, it is to be emphasized that development of seizures was mainly linked to a greater hourly drop of serum sodium at 24 h in relation to both admission and 6 h sodium levels (p=0.021 and 0.037, respectively, Table 3). Therefore, we believe that it is of utmost importance that patients showing a tendency for rapid drop of their serum sodium levels during the initial hours of intravenous fluid therapy to be followed more closely with a strict control of their sodium levels aiming to prevent further rapid drop. It is appreciated that the number of children developing seizures is too small to be statistically informative. However, this observation is in agreement with the general consensus.

The rapid drop of serum sodium level in children with DR-HD on receiving large volumes of NS for IVE can be explained by the fact that isotonic NS is actually relatively hypotonic compared to the high tonicity of serum of these patients especially those presenting with very high sodium levels on admission. This concept is shared by other authors who actually recommend the administration of a custom-made fluid with sodium content higher than that of NS for IVE in children with severe hypernatremia to avoid rapid drop of serum sodium levels when the relatively hypotonic NS is used for that purpose [17].

Table 2 Serum sodium on admission and the hourly drop rate in children with DR-HD classified by their IVE requirements

	No IVE (a) (n=11)	20 ml/kg IVE (b) (n=24)	≥40 ml/kg IVE (c) (n=13)	[a]p
Na−0 (mEq/L)	161.8 (160.4–166.2)	163.9 (160.9–166.0)	161.7 (160.4–164.9)	a–b=0.631
				a–c=0.685
				b–c=0.252
Hourly Δ Na 0–6 (mEq/L/h)	0.51 (0.46–0.54)	0.53 (0.483–0.61)	0.58 (0.53–0.64)	a–b=0.383
				a–c=0.013
				b–c=0.085
Hourly Δ Na 0–24 (mEq/L/h)	0.50 (0.46–0.57)	0.52 (0.473–0.57)	0.53 (0.46–0.56)	a–b=0.708
				a–c=0.663
				b–c=0.962

Data presented as median (IQR)

DR-HD diarrhea-related hypernatremic dehydration, *IVE* initial volume expansion, *Na−0* serum Na on admission, *Δ Na 0–6* drop of serum Na from admission to 6 h, *Δ Na* 0–24 drop of serum Na from admission to 24 h

[a] Mann–Whitney test

Large volumes of fluids used for initial volume resuscitation (≥40 ml/kg) were associated with increased likelihood of mortality. This association with mortality was not linked to the degree of dehydration on presentation as assessed by the attending physician or to the serum sodium level on admission. The cause of death in three out of the four children who succumbed was most probably related to neurological complications of hypernatremia or its management (one with intracranial bleeding and two with cerebral edema). The development of neurological deterioration prior to death, CT scan findings, relatively early death of these children on day 2 of PICU admission and absence of refractory shock or signs of volume overload make other causes of mortality unlikely. One patient who developed sudden unexplained asystole, also on day 2, could not be resuscitated. It is worth noting that the child who presented with intracranial bleeding had the highest serum sodium among the four children who succumbed and that the child with unexplained death received the largest volume for IVE among those children (patients 1 and 3 respectively in Table 5).

Hypernatremic dehydration is universally associated with high mortality rates especially in developing countries and was recently found to be an independent predictor of death in children with diarrhea [4]. The occurrence of death unrelated to neurological complications and lack of correlation between mortality and severity of hypernatremia are well described [13].

In this study, children who received 40 ml/kg or more for IVE were more likely to die with an OR of 3.3 (CI=1.5–7.2). A recently published large retrospective study of 97 children with hypernatremic dehydration found that using an initial fluid bolus was among the key factors in developing cerebral edema [5].

The difference in the mortality rate of hypernatremia between developing and developed countries can be accounted for by the underlying pathophysiology of hypernatremia where diarrhea is no longer a major cause of the condition in developed countries [12] and a possible delay both in seeking medical advice by parents and in referral of these children to hospital by primary health care providers because of the preservation of the intravascular volume till late stages. The difference in the

Table 3 Serum sodium on admission and the hourly drop rate in children with DR-HD classified by development of seizures during PICU stay

	No seizures (n=45)	Seizures (n=3)	[a]p
Na−0 (mEq/L)	162.7 (160.7–165.9)	163.6 (162.4–164.0)	0.831
Hourly Δ Na 0–6 (mEq/L/h)	0.52 (0.48–0.59)	0.58 (0.57–0.84)	0.084
Hourly Δ Na 0–24 (mEq/L/h)	0.51 (0.47–0.56)	0.65 (0.56–0.75)	0.021
Hourly Δ Na 6–24 (mEq/L/h)	0.51 (0.45–0.58)	0.63 (0.56–0.70)	0.037

Data presented as median (IQR)

DR-HD diarrhea-related hypernatremic dehydration, *Na−0* serum Na on admission, *Δ Na 0–6* drop of serum Na from admission to 6 h, *Δ Na 0–24* drop of serum Na from admission to 24 h

[a] Fisher's exact test

Table 4 Age, weight, degree of dehydration, IVE requirement, serum sodium on admission, and hourly drop rate of serum sodium level in children with DR-HD classified by PICU outcome

	Survived (n=44)	Succumbed (n=4)	p
Age (months)	19 (14.3–28)	10.5 (9–36.8)	0.287[a]
Weight (kg)	10.85 (9.9–13.0)	10.8 (8.8–13.6)	0.926[a]
Degree of dehydration			
Moderate	n=19 (43.2%)	n=2 (50%)	0.594[b]
Severe	n=25 (56.8%)	n=2 (50%)	
IVE			
0–20 ml/kg	n=34 (77.3%)	n=1 (25%)	0.055[b]
≥40 ml/kg	n=10 (22.7%)	n=3 (75%)	
Na−0 (mEq/L)	162.9 (160.6–165.8)	163.3 (161.9–176.3)	0.391[a]
Hourly Δ Na 0–6 (mEq/L/h)	0.53 (0.48–0.61)	0.57 (0.52–0.59)	0.422[a]
Hourly Δ Na 0–24 (mEq/L/h)	0.52 (0.48–0.57)	0.50 (0.42–0.62)	0.627[a]

Data presented as median (IQR) and number (in percent)

DR-HD diarrhea-related hypernatremic dehydration, *IVE* initial volume expansion, *Na*-0 serum Na on admission, *Δ Na* 0-6 drop of serum Na from admission to 6 h, *Δ Na* 0–24 drop of serum Na from admission to 24 h

[a] Mann–Whitney test

[b] Fisher's exact test

availability of resources between the two settings is also appreciated. The limitations posed by the small number of children who succumbed (n=4) in this study are acknowledged. Normal saline was previously found to be preferable to hypotonic saline in gastroenteritis treated with intravenous fluids as it prevented the development of hyponatremia in isonatremic children [16].

Some published mathematical formulas strive to calculate the rate of drop of serum sodium level over time in patients with hypernatremia taking in consideration, among others, the initial serum sodium level and the sodium content of the IV fluid used. Some of these formulas find NS to be too concentrated to cause a substantial decline in the serum sodium level in hypernatremia [1]. A recent article found currently available formulas unable to accurately predict changes in serum sodium levels in ICU settings [11].

From the satisfactory rate of drop of serum sodium level in the first 24 h, the low incidence of seizures (6.3%), and the relatively low mortality rate (8.4%) in this study of children with DR-HD in a developing country, we conclude that NS is a safe initial rehydration fluid for children with DR-HD requiring IV fluid therapy.

Judicious use of fluid boluses for IVE should be exerted as using larger volumes might be associated with higher drop of serum sodium at 6 h and possibly increased

Table 5 Characteristics of the four patients with DR-HD who succumbed during PICU stay

	Patient 1	Patient 2	Patient 3	Patient 4
Age (months)	45	9	9	12
Sex	Female	Male	Female	Female
Na−0 (mEq/L)	180.4	161.7	164.1	162.4
Hourly Δ Na 0–6 (mEq/L/h)	0.51	0.56	0.59	0.58
Hourly Δ Na 0–24 (mEq/L/h)	0.46	0.53	0.41	0.65
Hourly Δ Na 6–24 (mEq/L/h)	0.45	0.52	0.35	0.56
Serum potassium (mEq/L)	3.7	4.2	3.8	4.1
Degree of dehydration	Moderate	Moderate	Severe	Severe
IVE requirement (ml/kg)	0	40	60	40
Amount of deficit therapy (ml/kg/day)	35	40	50	50
Time of death	Day 2	Day 2	Day 2	Day 2
Proposed cause of death	Intracranial hemorrhage	Cerebral edema	Unexplained death	Cerebral edema

DR-HD diarrhea-related hypernatremic dehydration, *Na−0* serum Na on admission, *Δ Na 0–6* drop of serum Na from admission to 6 h, *Δ Na 0–24* drop of serum Na from admission to 24 h, *Δ Na* 6–24 drop of serum Na from 6 to 24 h post-admission, *IVE* initial volume expansion

mortality. The subsequent fluid management of children with DR-HD after 24 h of IV rehydration should vary depending on the child's ability to tolerate enteral fluids.

The authors do not recommend withholding necessary fluid boluses for IVE in children with DR-HD who are hemodynamically unstable. The recommendation is to use fluid boluses after careful consideration and to closely monitor those children with DR-HD requiring large volumes for IVE preferably in a PICU setting.

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