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Management of hyponatremic seizures in children with hypertonic saline: A safe and effective strategy

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Objective: **To study efficacy and safety of hypertonic saline administration in the management of hyponatremic seizures.**

Design: **Retrospective, observational, cross-sectional study with factorial design.**

Setting: **In-patient population in a university hospital.**

Patients: **All children admitted with serum sodium concentrations <125 mmol/L. Sixty-nine episodes of severe hyponatremia in 60 children were reviewed. Forty-one of these children presented with seizures.**

Interventions: **Twenty-five of 41 seizure patients received an iv bolus of 4 to 6 mL/kg body weight of 3% saline. Twenty-eight patients were treated with a benzodiazepine and/or phenobarbital with or without the subsequent administration of hypertonic saline.**

Measurements and Main Results: **Thirteen treatment failures and ten instances of apnea occurred among the 28 patients treated with benzodiazepine/phenobarbital. Administration of hypertonic saline resulted in resolution of seizures and apnea in all cases. Those patients receiving 3% saline had a higher serum sodium increase rate from 0 to 4 hrs than the remaining patients (3.1 ± 1.3 vs. 1.7 ± 1.2 mmol/L·hr, $p < .01$). None developed subsequent neurologic deterioration or clinical manifestations of osmotic demyelination syndrome.**

Conclusion: **Treatment of hyponatremic seizures with routine anticonvulsants may be ineffective and is associated with a considerable incidence of apnea. A rapid increase in the serum sodium concentration by 3 to 5 mmol/L with the use of hypertonic saline is safe and efficacious in managing acute symptomatic hyponatremia. (Crit Care Med 1991; 19:758)**

KEY WORDS: **hyponatremia; seizures; demyelination; anticonvulsants; saline solution, hypertonic; central nervous system; patient outcome assessment; sodium**

Hyponatremia is one of the most commonly encountered electrolyte abnormalities in hospitalized patients (1). The gradual development of hyponatremia may not result in neurologic dysfunction, even at serum sodium levels <110 mmol/L (1, 2). However, a precipitous decrease in serum sodium concentration can result in extensive brain damage and death in previously healthy adults and children (3–5). Hyponatremia is also the most frequent cause of nonfebrile seizures in children <2 yrs of age (6). Hyponatremic seizures were described in infants after ingestion of large amounts of water (7–10).

Prompt correction of hyponatremia in symptomatic patients to prevent progression of central nervous system (CNS) dysfunction has been advocated (4, 11). However, several investigators (12–16) emphasized that correction of sustained hyponatremia at a rapid rate (>0.5 mmol/L·hr) may be more deleterious than hyponatremia itself, and may result in central pontine and extrapontine myelinolysis. The efficacy and safety of various therapeutic regimens in children with symptomatic hyponatremia have not been described. The objective of this clinical study was to review our experience with hyponatremia in children regarding management and outcome.

MATERIALS AND METHODS

We retrospectively studied the medical records of all children who were admitted with, or who subsequently developed, severe hyponatremia (serum sodium <125 mmol/L) during their hospitalization over a 5-yr period from 1984 to 1989. Age, sex, and temperature on hospital admission were noted. The etiology of hyponatremia and the patient's hydration status were determined on the basis of history,

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physical examination, associated medical/surgical illness, and relevant laboratory findings. The syndrome of inappropriate antidiuretic hormone was defined according to previously described criteria (17, 18). These criteria included serum osmolality <270 mosm/kg, absence of clinical evidence of fluid depletion, urine osmolality >250 mosm/kg, and normal blood urea nitrogen concentration. Serum sodium level on admission, presence of seizures, anticonvulsant treatment and response, and administration of hypertonic saline and response were noted. Hypertonic saline treatment when administered consisted of 4 to 6 mL/kg body weight of 3% sodium chloride as a rapid iv bolus. Due to the retrospective nature of the study, the indications for, and the timing of, hypertonic saline administration may have varied among patients. Serum sodium levels were recorded when obtained (±30 mins) at 4, 8, 12, 24, and 48 hrs. The rates of increase in serum sodium from 0 to 4 and 0 to 24 hrs were calculated based on laboratory values at these times. Subsequent clinical course and neurologic examination on hospital discharge were noted.

Statistical Analysis. Initial serum sodium concentrations in patients with and without seizures were compared by *t*-test. Serum sodium levels at various time intervals in patients receiving hypertonic saline were compared by repeated-measures analysis of variance with levels in patients not receiving hypertonic saline. The rates of serum sodium increase from 0 to 4 and 0 to 24 hrs in these two groups were compared by *t*-test. Data are expressed as mean ± SD and a $p < .05$ was considered significant.

RESULTS

There were a total of 69 admissions for hyponatremia in 60 patients. The mean age of all patients was 23 ± 43 months (range 3 wks to 16 yrs), while the mean age for those patients with seizures was 10 ± 22 months (range 4 wks to 12 yrs). Most patients were afebrile with a mean temperature of 36.3 ± 1.5°C. Hydration status was considered normal in 52 patients, while 15 patients were considered mildly dehydrated and two moderately dehydrated. Forty-one (60%) of 69 hyponatremic episodes were associated with seizures. There was no significant difference in the initial serum sodium value in episodes with or without seizures (119 ± 5 vs. 120 ± 4 mmol/L).

The etiology of hyponatremia and associated prevalence of seizures are shown in Table 1. A recent history of excessive oral water intake was the most common cause of hyponatremia, and all these patients presented with seizures. GI losses, syndrome of inappropriate antidiuretic hormone, renal failure, cystic fibrosis, diuretic therapy, adrenal insufficiency, and epidermolysis bullosa were other conditions leading to hyponatremia with a varying prevalence of seizures among them. Although we could not accurately determine the duration of hyponatremia, conditions in which hyponatremia could be expected to be more acute had a higher prevalence of seizures than those conditions where hyponatremia would likely have developed gradually.

Table 1. Etiology of hyponatremia with prevalence of seizures

	N	Seizures
H_2O intake increase	27	27
GI losses	11	6
SIADH	10	6
Renal disease	5	1
Cystic fibrosis	5	0
Diuretic therapy	4	0
Adrenal insufficiency	3	0
Epidermolysis bullosa	1	0
Unknown	3	1
Total	69	41

N, number of admissions; SIADH, syndrome of inappropriate antidiuretic hormone.

Of the 41 episodes of hyponatremic seizures, six resolved spontaneously. Seven patients received hypertonic saline alone, resulting in immediate seizure control. Twenty-eight episodes of seizures were initially treated with phenobarbital and/or a benzodiazepine. Seizures resolved in 15 of these episodes. However, there were six instances of apnea, necessitating endotracheal intubation and mechanical ventilation. (In nine of these 15 episodes, hypertonic saline was administered with resolution of symptoms in the six apneic patients.) The remaining 13 episodes of seizures were unresponsive to phenobarbital and benzodiazepine therapy, with four patients becoming apneic while still continuing to convulse. Nine children in this group were treated with hypertonic saline with immediate resolution of apnea and/or seizures, while the other four patients not so treated had prolonged seizures. In total, 25 patients received a bolus of hypertonic saline with prompt reversal of symptoms. Hyponatremic patients not treated with hypertonic saline were managed with 0.9% sodium chloride infusion and fluid restriction.

In patients presenting with seizures, serum sodium levels were not significantly different for those patients treated with hypertonic saline (n = 25) and those patients not so treated (n = 16) at 0, 4, 8, 12, 24, and 48 hrs (Fig. 1). The serum sodium increase rate from 0 to 4 hrs was significantly ($p < .01$) higher in patients treated with 3% sodium chloride than in

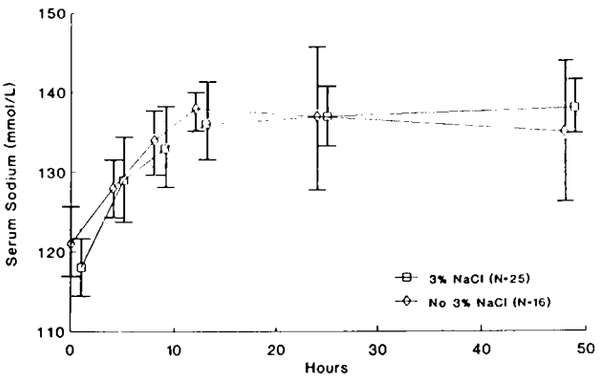

Figure 1. Serial serum sodium concentrations in seizure patients treated with and without hypertonic saline.

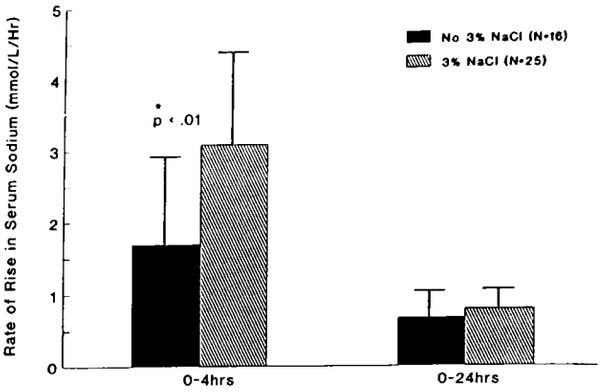

Figure 2. Serum sodium increase rates at 0 to 4 and 0 to 24 hrs in seizure patients treated with and without hypertonic saline.

those patients not so treated (3.1 ± 1.3 vs. 1.7 ± 1.2 mmol/L·hr) (Fig. 2). However, there was no significant difference in the serum sodium increase rate from 0 to 24 hrs between these two groups (0.8 ± 0.3 vs. 0.7 ± 0.3 mmol/L·hr). In both groups, serum sodium increase rates have been previously characterized in the literature as rapid (>0.5 mmol/L·hr).

All children were observed for ≥4 days after correction of hyponatremia. None developed CNS deterioration or clinical signs of osmotic demyelination syndrome. All patients had recovered their premorbid neurologic status at the time of discharge.

DISCUSSION

Acute symptomatic hyponatremia is commonly encountered in children. Excessive ingestion of water appears to be the most common cause of hyponatremic encephalopathy in infants (6–10). Such children may present with stupor, coma, and seizures (11). The mechanism of hyponatremia after excessive ingestion of water in otherwise healthy infants with normal renal function is unclear. Linshaw et al. (19) suggested an abnormal parent-infant relationship, with oral gratification received from sucking on a bottle of water as an explanation of infantile psychogenic water drinking. Excessive oral water intake from overdiluted formulas, fruit juices, or soft drinks was the most common cause of symptomatic hyponatremia in our patients. Arieff and Fraser (5) described severe symptomatic hyponatremia in previously healthy children who were hospitalized for minor illness or routine surgery. Inappropriate fluid administration in patients who were at risk for the syndrome of inappropriate antidiuretic hormone was felt to be responsible for their hyponatremic encephalopathy.

The most important clinical consequences of severe hyponatremia and its treatment involve the CNS. Arieff and Fraser (3, 5) described seizures, cerebral edema, brainstem herniation, permanent brain damage, respiratory arrest, and death from severe untreated hyponatremia of rapid onset. Early recognition and rapid correction of markedly low serum sodium concentrations in symptomatic patients to mildly hyponatremic levels by the administration of hypertonic saline have been considered important in reducing potential mortality and morbidity (4, 11). However, Sterns (2) showed that severe sustained hyponatremia can be well tolerated, with the prognosis primarily dependent on the underlying disease entity associated with hyponatremia. Rapid correction of hyponatremia in such patients is fraught with the potential complication of central pontine and extrapontine myelinolysis clinically manifesting as spastic quadriplegia, pseudobulbar palsy, decreasing level of consciousness, and behavioral changes without focal findings (12, 13). Therefore, the management of severe hyponatremia poses a major dilemma for the clinician (20, 21).

The apparent discrepancies in clinical observations and management recommendations among various studies can be explained by the response of the CNS to its changing osmolal environment. Laboratory experiments (16) demonstrated that acute hyponatremic encephalopathy is associated with an increase in brain water content. Autopsy findings in fatal cases of acute water intoxication have included cerebral edema with uncal and brainstem herniation (5, 22). Consequently, rapid correction of the serum sodium level in acutely hyponatremic patients would be expected to decrease brain water and restore CNS function. However, with chronic hyponatremia, the brain water content tends to normalize with time. Sterns et al. (16) showed that the increase in brain water content in hyponatremic rats is less than what

would be predicted by the extent to which the extracellular fluid osmolality is decreased. A rapid loss of brain sodium and potassium is followed by delayed depletion of nonelectrolyte solute. This osmoregulatory mechanism allows the brain to normalize its water content when faced with sustained hyponatremia. In these situations, rapid correction of hyponatremia with hypertonic saline results in severe neurologic abnormalities and development of demyelinating lesions in the central pons, thalamus, internal capsule, cerebellum, and cerebral hemispheres (12–16). In this context, correction of serum sodium at a rate >0.5 mmol/L·hr has been considered too rapid (12–14).

The distinction between acute and chronic hyponatremia is arbitrary, since the time frame during which brain water content is normalized in human subjects is not established. Additionally, it is often impossible to determine accurately the duration of hyponatremia in patients in whom previous serum sodium determinations are not available. The distinction should therefore be made between symptomatic and asymptomatic hyponatremia, rather than emphasizing its duration. In our series, seizures occurred in patients in whom hyponatremia could have been expected to be relatively recent. The use of routine anticonvulsants was not consistently effective in managing hyponatremic seizures, and was associated with the frequent occurrence of respiratory depression requiring mechanical ventilation. Treatment with a rapid iv bolus of 4 to 6 mL/kg body weight of 3% saline promptly controlled seizures and respiratory depression with or without prior anticonvulsant administration. With 0.6 L/kg body weight as the apparent volume of distribution for sodium, one could anticipate an immediate increase of 3 to 5 mmol/L serum sodium concentration in these patients. This relatively small but rapid increase in serum sodium appears to be effective in reversing the CNS manifestations of symptomatic hyponatremia. The administration of 29.2% saline aimed at a similar increase in serum sodium was also shown to be effective in treating hyponatremic seizures in adults (23). After this acute increase, further restoration of serum sodium occurs mainly by water diuresis, especially in infantile water intoxication as described by Medani (10). Although our patients treated with hypertonic saline showed a greater immediate (0 to 4 hrs) increase in serum sodium, the rate of increase over a 24-hr period was not significantly different in the two groups.

The clinical manifestations of central pontine and extrapontine myelinolysis are considered highly stereotypic, occur within 1 to 4 days after admission, and are reported to be associated with an increase in serum sodium of >0.5 mmol/L·hr (12, 13). The serum sodium concentration increase rate in our patients treated with and without hypertonic saline was higher than this rate, at both 0 to 4 and 0 to 24 hrs. We did not encounter any patient who developed the previously described clinical signs of osmotic demyelination syndrome. The "rapid" increase in serum sodium was thus both therapeutically effective as well as clinically well tolerated. The rapid increase in serum sodium in the acute phase of therapy was to a level that was still in the mildly hyponatremic range, and this increase was over a relatively short (4 hrs) period of time. The subsequent serum sodium increase rate was less rapid. We speculate that symptomatic hyponatremia in these children is relatively acute and is associated with increased brain water. A rapid increase in serum sodium level in such patients results in normalization of brain water content. On the other hand, chronic asymptomatic hyponatremia is encountered when the CNS osmoregulatory mechanism has already normalized brain water content, and in these situations, a rapid increase of serum sodium could be hazardous.

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Editorial Approach

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