Evidence for Managing Hypernatremia
Is It Just Hyponatremia in Reverse?

Richard H. Sterns

Clin J Am Soc Nephrol 14: 645–647, 2019. doi: https://doi.org/10.2215/CJN.02950319

Acute hyponatremia or hypernatremia can cause brain damage. Correcting chronic hyponatremia or hypernatremia too aggressively can do the same. A rapidly falling plasma sodium concentration causes cerebral edema; a rapidly rising concentration causes osmotic demyelination (1). There is an appealing symmetry to these observations, and they serve as underpinnings for widely accepted recommendations for managing patients with abnormal sodium concentrations. However, evidence supporting these guidelines is far from symmetrical. Although controlled trials are lacking, recommendations for managing hyponatremia rest on robust data from animal models, several observational series, and hundreds of patient reports (2). By contrast, when it comes to treating hypernatremia, we are on much shakier ground.

In this issue of the *Clinical Journal of the American Society of Nephrology*, Chauhan *et al.* (3) challenge the idea that rapid correction (defined as >0.5 mEq/L per hour or >12 mEq/L in 24 hours) causes neurologic injury in hypernatremic adults. Using the Medical Information Mart for Intensive Care-III, the investigators identified 122 patients who were admitted to the hospital with serum sodium concentrations >155 mEq/L and 327 patients whose serum sodium rose to >155 mEq/L while in the hospital. Of the patients with hospital-acquired hypernatremia, 128 were considered "chronic," because the disturbance developed over >48 hours. The hourly rate of correction was computed from the time required to lower the serum sodium from its peak to a level of <145 mEq/L. The daily rate of correction was calculated from the fall in serum sodium levels over the first 24 hours. Correction rates were >0.5 mEq/L per hour in 32 of the patients who were hypernatremic on admission (likely due to a chronic disturbance) and 122 patients with hospital-acquired hypernatremia (both acute and chronic). Mortality rates were no different in patients who were rapidly corrected and patients who were slowly corrected. A review of ICD9 (International Classification of Diseases, Ninth Revision) codes, imaging reports, and discharge summaries failed to identify any patient who developed seizures or cerebral edema during correction of hypernatremia. Similarly, a manual review of daily progress notes available for 46 of the patients who were chronically hypernatremic found no evidence of neurologic morbidity related to rapid correction.

Although it could be argued that the number of patients with severe chronic hypernatremia who were rapidly corrected was too small to completely exclude the possibility of harm from rapid correction or that the study's methodology could miss subtle neurologic injury, these findings should prompt us to review the evidence supporting current therapeutic recommendations.

Current recommendations for the treatment of hypernatremia in adults are derived from observations in the pediatric literature (4–6). Among infants with hypertonic dehydration, rehydration seizures due to cerebral edema commonly develop in the first 24 hours of treatment. The likelihood of seizures is unrelated to the severity of hypernatremia, but it increases with more rapid rates of correction. The clinical impression that rehydration seizures are iatrogenic therapeutic complications has been verified in animal models.

In 1979, Kahn *et al.*(4) found that correction averaged 1.022±0.128 mEq/L per hour in nine newborns with rehydration seizures compared with 0.618±0.083 mEq/L per hour in 22 newborns who remained free of seizures. All infants with convulsions had been corrected by >0.7 mEq/L per hour. On the basis of these retrospective findings, rehydration regimens were altered. Subsequently, there were no seizures in 27 patients corrected by ≤0.5 mEq/L per hour (4,5). A more recent series from China reported that 49 of 97 infants who were hypernatremic developed cerebral edema during treatment manifest by seizures, papilledema, and in most patients, a bulging fontanelle (6). The rate of correction was 1.0±0.3 mEq/L per hour in the 49 patients with cerebral edema and 0.5±0.1 mEq/L per hour in the 39 patients who recovered uneventfully.

Although often cited to support a daily correction limit of 12 mEq/L, none of these studies showed that correction by >12 mEq/L commonly results in seizures; rather, they suggest that seizures are much less common (in fact, in the investigators' experience, nonexistent) when correction is ≤12 mEq/L per day. Thus, this rate of correction seems to be "safe" for dehydrated infants. Most reports of rehydration seizures have occurred in infants corrected at rates exceeding the "safe rate" by at least 50%, but the precise "harmful rate" was never defined.

Division of Nephrology, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester New York; and Rochester General Hospital, Rochester, New York

Correspondence:
Dr. Richard H. Sterns, Rochester General Hospital, 1425 Portland Avenue, Rochester, NY 14621. Email: richard.sterns@rochesterregional.org

There has not been a single convincing published report of cerebral edema after rapid correction of chronic hypernatremia in an adult. However, out of an abundance of caution, the safe rate for infants became enshrined in therapeutic recommendations for adults along with advice to correct by ≤10 mEq/L per day to avoid overshooting the mark. These standards mirror guidelines for correction of hyponatremia.

Although symmetry is appealing, the biologic mechanisms underlying complications of rapid correction of hyponatremia and hypernatremia are quite different. The main similarity is that both are consequences of adaptive changes in cellular contents of nonperturbing solutes known as organic osmolytes in response to osmotic stress (1). In chronic hyponatremia, cellular organic osmolytes are lost passively through a common channel, allowing equality of plasma and cell osmolalities without increased cell water. In chronic hypernatremia, specific transporters are upregulated, actively accumulating organic osmolytes that protect cells from dehydration. The adaptation to hyponatremia occurs more rapidly than adaptation to hypernatremia.

Cerebral edema after rapid correction of hypernatremia is caused by delayed shedding of accumulated organic osmolytes (likely because of persistently upregulated transporters). Cells with a surfeit of organic osmolytes swell when the serum sodium concentration falls, and cerebral edema occurs in the first 24 hours of rehydration. Cerebral edema is more dangerous in young children whose brains fill their cranial vaults than in older adults with cerebral atrophy.

Osmotic demyelination after rapid correction of chronic hyponatremia occurs, because reuptake of organic osmolytes takes place over several days. Astrocytes depleted of organic osmolytes are susceptible to dehydration, molecular crowding, damage to proteins and nucleotides, and resultant apoptosis when the serum sodium concentration rises too rapidly (7). The neurologic consequences of this injury, which reflect demyelination, do not become apparent for several days after correction of hyponatremia (1,2).

Rarely, acute hypernatremia, in most patients caused by unreplaced water losses from complete diabetes insipidus or severe hyperglycemia, can also result in osmotic demyelination (8). Because this complication also reflects molecular crowding, which leads to delayed cell death, the consequences of this injury may not become apparent until after hypernatremia has been treated. This delay and the quest for symmetry have led authors of a few patient reports to the erroneous conclusion that osmotic demyelination can be caused by rapid correction of either hyponatremia or hypernatremia.

Inadvertent rapid correction of chronic hyponatremia is common. If the ability to excrete dilute urine is restored during treatment, the ensuing water diuresis can increase serum sodium concentration by >2 mEq/L per hour (1,2). In some patients, osmotic demyelination can occur if correction exceeds 8 mEq/L per day. For this reason, patients with very low serum sodium concentrations should be cared for in settings that allow for meticulous monitoring of urine output and serum sodium levels. In patients with conditions placing them at high risk for osmotic demyelination, therapeutic relowering of the serum sodium concentration is recommended if inadvertent overcorrection occurs; this maneuver has been shown to be beneficial in animal models.

Inadvertent rapid correction of hypernatremia is much less likely, because the decrease in serum sodium concentration results primarily from intravenous fluids rather than urinary losses. If we accept that rapid correction is rarely, if ever, harmful in adults, we should be more comfortable treating severe chronic hypernatremia outside of critical care units. Although the risk of excessive correction has not been proven, some may still choose to aim for a daily correction rate of roughly 12 mEq/L. If this rate is inadvertently exceeded, however, we should definitely resist our yearning for symmetry and forego therapeutic reraising of the serum sodium concentration.

Although there may be no need for obsessive monitoring of the serum sodium concentration to avoid rapid correction of hypernatremia, careful monitoring is required in patients who are acutely hypernatremic with ongoing urinary water losses to avoid a further rise in serum sodium. Rapid infusion of 3% saline can be lifesaving in acute hyponatremia. We do not know if rapid infusion of electrolyte-free water is beneficial in acute hypernatremia, but it makes sense, because we know that at least some adults develop osmotic demyelination when the serum sodium rapidly rises to very high levels (8).

A few patient series have shown that extremely slow rates of correction of chronic hypernatremia are associated with higher mortality in adults (9,10). These findings are hard to interpret, because most patients with chronic hypernatremia are too sick to replace their water losses; the responsible underlying conditions are often fatal. There is no evidence that slow correction of chronic hypernatremia results in brain damage in either humans or experimental models.

Hyponatremia and hypernatremia are both disorders of plasma sodium, but the similarities end there. Although symmetry is appealing, we cannot apply what we know about sodium levels that are too low to the management of sodium levels that are too high.

Disclosures

None.

References

1. Sterns RH: Disorders of plasma sodium--causes, consequences, and correction. *N Engl J Med* 372: 55–65, 2015
2. Sterns RH: Treatment of severe hyponatremia. *Clin J Am Soc Nephrol* 13: 641–649, 2018
3. Chauhan K, Pattharanitima P, Patel N, Duffy A, Saha A, Chaudhary K, Debnath N, Van Vleck T, Chan L, Girish N, Coca S: Rate of correction of hypernatremia and health outcomes in critically ill patients. *Clin J Am Soc Nephrol* 14: 656–663, 2019
4. Kahn A, Brachet E, Blum D: Controlled fall in natremia and risk of seizures in hypertonic dehydration. *Intensive Care Med* 5: 27–31, 1979
5. Blum D, Brasseur D, Kahn A, Brachet E: Safe oral rehydration of hypertonic dehydration. *J Pediatr Gastroenterol Nutr* 5: 232–235, 1986
6. Fang C, Mao J, Dai Y, Xia Y, Fu H, Chen Y, Wang Y, Liu A: Fluid management of hypernatraemic dehydration to prevent cerebral oedema: A retrospective case control study of 97 children in China. *J Paediatr Child Health* 46: 301–303, 2010

7. Gankam Kengne F, Decaux G: Hyponatremia and the brain. *Kidney Int Rep* 3: 24–35, 2017
8. Shah MK, Mandayam S, Adrogué HJ: Osmotic demyelination unrelated to hyponatremia. *Am J Kidney Dis* 71: 436–440, 2018
9. Alshayeb HM, Showkat A, Babar F, Mangold T, Wall BM: Severe hypernatremia correction rate and mortality in hospitalized patients. *Am J Med Sci* 341: 356–360, 2011
10. Bataille S, Baralla C, Torro D, Buffat C, Berland Y, Alazia M, Loundou A, Michelet P, Vacher-Coponat H: Undercorrection of hypernatremia is frequent and associated with mortality. *BMC Nephrol* 15: 37–46, 2014

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, "Rate of Correction of Hypernatremia and Health Outcomes in Critically Ill Patients," on pages 656–663.