MAYO CLINIC

Hyponatremia Management: Walking the Tightrope Without a Net

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In this issue of *Mayo Clinic Proceedings*, Geoghegan et al[1] provide the hospital medicine community with valuable insights into the real-world management of severe hyponatremia. Hyponatremia is the most common, and arguably the most difficult to interpret and manage, electrolyte imbalance seen in the inpatient environment.[2,3] Correctly managing this potentially life-threatening disorder demands a deft touch. Correct interpretation of often-conflicting clinical examination findings while understanding the unique pathophysiology each patient illustrates is essential, even before engaging a treatment algorithm. Few conditions require such prolonged intensive acute monitoring to balance the prevention of catastrophic outcomes resulting from (1) failing to adequately correct the initial presenting condition versus (2) overzealous correction of the condition.

Diagnosis of the causative factors and treatment of severe hyponatremia (<120 mmol/L) requires the quick assessment of hyponatremia's risk of leading to clinically dangerous cerebral edema while formulating a strategy to correct the underlying cause and promote a safe rate of correction of the serum sodium. Complicating matters further are pseudohyponatremia and hyponatremia associated with hyperosmolality, such as that resulting from hyperglycemia and infusions of mannitol. Differentiation of whether the hyponatremia is triggered primarily from decreased effective circulating volume leading to antidiuretic hormone release versus other nonosmotic stimuli leading to an antidiuretic hormone effect has been one of the traditional "two first questions" one asks when encountering severe hyponatremia. The partner question of whether the patient is symptomatic as a result of the hyponatremia often turns out to be much less straightforward than one might imagine. The accompanying clinical scenarios associated with hyponatremia often come with their own set of clinical symptoms and by themselves are competing issues for morbidity, mortality, and often-severe clinical symptoms.

Geoghegan et al[1] take a novel approach to the study of this vexing and dangerous clinical condition of an admission serum sodium concentration of less than 120 mmol/L. Rather than focusing on the varying levels of correction rates and their impacts, the authors chose to evaluate the impact of suboptimal correction rates of serum sodium concentration (<5 mmol/L or >10 mmol/L) on outcomes that occurred within the initial 24 hours of admission. We are provided outcomes data on a 4-year (2008-2012) retrospective cohort treated at a tertiary referral center, including only those patients who had hyponatremia on admission, not as a new condition acquired during hospitalization. Primary outcomes of this study included the impact of optimal versus suboptimal sodium correction on the development of osmotic demyelination syndrome (ODS), hospital death, and length of intensive care unit and hospital stay. We are provided a breakdown of the 412 patients included in this study by optimal correction in 24 hours (n=211 [51%]), undercorrection at 24 hours (n=87 [21%]), or overcorrection (n=114 [28%]).

The real-world nature of this study is illustrated by the authors' utilization of a calculation of the serum sodium value closest to the 24-hour mark, which allowed correction for values drawn before or after, but within approximately 3 hours of, the 24-hour measurement. This issue does detract from the ability to make definitive conclusions on the basis of the association of outcomes with the correction rate.

Is the authors' chosen definition of optimal sodium correction defensible? Many recall the guidelines of correction rates of less than 12 mmol/L over 24 hours. These were derived from historical cohorts, which illustrated no episodes of the then-named central pontine myelinolysis when sodium correction rates were below this value range.[4] More recent data have suggested that the rate of correction should be even less rapid, with rates of 4 to 6 mmol/L over 24 hours being recommended among symptomatic patients who have serum sodium levels of less

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than 120 mmol/L.[5,6] However, what of the ongoing potential risks of cerebral edema potentiated by inadequate sodium correction? Mortality risks have been associated with undercorrection in the literature; however, separating the inciting and interrelated factors associated with undertreated hyponatremia—for example, central nervous system trauma, neurologic stroke, and do-not-resuscitate status—has remained a difficult issue.[6,7] Recent guidelines would seem to suggest that Geoghegan et al[1] have indeed applied a well-reasoned definition.[5,8]

The cohort was one with whom clinicians are likely familiar, with a dramatic set of complicating medical conditions. Charleston scores (ie, an assessment of severe medical comorbidity) averaged 5 (range, 3-7), 42% required intensive care unit admission, 33% had a diagnosis of congestive heart failure, 31% had either chronic or acute kidney disease or injury, 16% had alcoholism, and 7% had cirrhosis. The 3 groups were not significantly different with respect to comorbidities or most of the other clinical factors. There are omissions from the authors' data set, however.

The multifactorial association of causation and outcomes among patients with malignancy and hyponatremia is well known. However, we are not made aware of the number of patients with malignancy in the cohort. The authors assessed the utilization of thiazide diuretics and selective serotonin reuptake inhibitor agents but failed to assess the utilization of opioids or other analgesics such as nonsteroidal anti-inflammatory drugs. The latter analgesics could be important because patients with medication-induced severe hyponatremia, without other compounding clinical situations, have been suggested to be at lower risk.[6] The analysis would also have benefited from tracking surgical interventions in the cohort.

Despite the severity of hyponatremia in this cohort, combined with the dramatic comorbidities, overall outcomes were not different among the 3 groups; that is, the overall cohort survival to discharge was 94% and not different among the 3 groups. The mortality rate is concordant with that in other studies.[6] Osmotic demyelination syndrome was noted in but one patient in the overcorrection group and not seen in the remainder of the cohort. The rate of ODS of less than 1% is quite strikingly low. A major strength of the study is the prolonged (6-month) extension of the chart reviews among the participants to rule out ODS.

There was a substantial increase in hospital length of stay among the group who was undercorrected. This issue leads to speculation of whether there is hidden risk to undercorrection. The potential that undertreated sodium levels led to persistent cerebral edema or other hyponatremia-related conditions remains unclear. Although the authors tracked seizures in the cohort, they did not track other neurologic symptoms. Cardiovascular dysfunction, falls, and fracture risk have been suggested to be independently related to hyponatremia as well, which could play a role in the apparent deleterious results of inadequate correction.[9-11]

WHAT ARE BUSY CLINICIANS TO TAKE AWAY FROM THIS STUDY?

A crucial point needs to be considered before we leap to acceptance of it being "OK to miss the targets." This study's cohort was accrued before more contemporary hyponatremia treatment guidelines. Previously, clinicians were faced with the daunting task of distinguishing the etiology of severe hyponatremia in somewhat black and white terms: namely, whether the patient was euvolemic or had decreased circulating blood volume. This distinction can be extremely challenging even for experienced clinicians. Historically, treatment strategies were then largely based on calculation of free water excess or sodium deficits. These complex calculations were then followed by treatment calculations that often required tracking of not only the serum sodium but also the urine osmolality and solute intake as crucial components of the regimen required to reach the desired correction targets. It is then easy to understand how a group of motivated, experienced clinicians in a tertiary referral center failed to achieve the desired sodium correction rates.

The contemporary guidelines that are summarized as administration of 100- to 150-mL aliquots of 3% saline in response to symptomatic severe hyponatremia, with repetition based on symptomatic assessments every 10 to 30 minutes, and arginine vasopressin "rescue" if overcorrection is noted, will deserve evaluation on a large scale.[5,8,12] Conservative management approaches for asymptomatic patients, without life-threateningly low serum sodium values, should still be pursued along with use of sound clinical judgment. The

reversal of the precipitating causes continues to be a prime directive and should not be forgotten in a protocol-driven environment.

Finally, the issue of what risks are incurred by undercorrection deserves specific further attention, but correction of sodium by 4 to 6 mmol in 24 hours appears to be efficacious.[1,5,6,8]

In the practice of hospital medicine, the sodium-management tightrope is unavoidable and oftentimes must be traversed. Clinicians are warned to move slowly and balance well.

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