Clinical Chemistry

Osmotic Demyelination Syndrome in Hyponatremia: Does the Rate of Sodium Correction Matter?

Article:
Supawadee Suppadungsuk and Kianoush Kashani.
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Clin Chem 2024; 70(7): 894–6. https://doi.org/10.1093/clinchem/hvae010

Guest: Dr. Supawadee Suppadungsuk is from Ramathibodi Hospital, Mahidol University in Bangkok, Thailand and is a postdoctoral researcher at the Mayo Clinic in Rochester, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Hyponatremia, or a low plasma sodium concentration, is frequently encountered in hospitalized patients. When confronted with this scenario, the task of the care team is to administer saline and other medications to raise the plasma sodium value. However, increasing plasma sodium too quickly can result in osmotic demyelination syndrome, or ODS, which can cause extensive destruction of brain tissue or even death. For this reason, conventional wisdom dictates that plasma sodium concentrations must be increased gradually, allowing neurons to incrementally adjust to the changing electrolyte content of the surrounding fluid. But what if conventional wisdom is wrong and the rate of sodium correction isn't the primary determinant of ODS? What are the findings of recent studies and what are the implications for clinical practice?

A new perspective article appearing in the July 2024 issue of *Clinical Chemistry* highlights a recent publication on osmotic demyelination syndrome and suggests the standard approach to the management of hyponatremia may need to change. In this podcast, we are excited to speak with the article's lead author. Dr. Supawadee Suppadungsuk is a nephrologist from Ramathibodi Hospital, Mahidol University in Bangkok, Thailand and a postdoctoral researcher at the Mayo Clinic in Rochester, Minnesota. Doctor, your article discusses whether the rate of treatment matters in hyponatremia and osmotic demyelination syndrome, or ODS. Can you explain what hyponatremia and ODS are and why they are significant?

Supawadee Suppadungsuk: Thank you for your question, Bob. Hyponatremia is a common electrolyte disorder in hospitalized patients, defined as blood sodium level lower than 135 millimoles per liter. The incident of hyponatremia ranges of 5% to 35% among inpatients and outpatients. Patient may be asymptomatic or may have severe neurological and life-threatening conditions such as seizures or coma when the hyponatremia is severe, or it happens too acutely. That's why it's crucial to treat symptomatic patient immediately.

Clinicians are also concerned about complications known as of osmotic demyelination syndrome, we call ODS, that can alter if hyponatremia isn't treated accurately. ODS is rare, but this condition can cause serious neurological symptoms such as body paralysis, seizure, or coma. The incident rate was reported less than 0.5%. This term was linked to patient who developed central pontine myelinolysis due to chronic hyponatremia and had rapid sudden correction since 1980s. A recent large cohort study by Dr. Macmillan and team evaluated ODS and hyponatremia patients published in *New England Journal Medicine Evidence*. The result shown that the incident of ODS was very low, only 0.5%, and around 58% of ODS patients did not experience a rapid sodium correction.

Bob Barrett: Doctor, can you summarize the key findings from the study by Dr. MacMillan regarding ODS incidence and sodium correction rate? How will the results contribute to our understanding of ODS?

Supawadee Suppadungsuk: So, more detail in this study, Dr. MacMillan and team did a multicenter cohort study across five academic hospitals in Canada for almost 11 years. From 2010 to 2020, using the general medicine inpatient database, they evaluated over 22,000 hospital admissions with hyponatremia with an initial serum sodium lower than 130 millimole per liter. The primary outcome was to evaluate the incident of ODS by reviewing imaging data and medical records using the ICD-10 code. Their secondary aim was the rate of rapid correction of serum sodium, which is defined as an increase in serum sodium greater than 8 millimoles per liter within 24 hours.

The interesting result found that only 12 patients of the entire cohort developed ODS with an incidence only 0.05% among patients who were exposed to rapid rate correction more than 8. ODS altered at 0.14% in a subgroup of patients with serum sodium below 120. The incident rate of ODS was only 0.3%. However, if you look at a patient who had initial serum sodium less than 110 millimoles per liter, the incidence of ODS significantly increase to 2.6%.

It should be noted that the majority of patients in this study had mild hyponatremia with over 80% having serum sodium above 120 millimoles per liter. The average initial serum sodium was 120 millimoles per liter. This means that the study population had a lower list of ODS. They also noted that 17.7 of the cohort experience a rapid sodium correction rate. Furthermore, almost 70% of patient with initial serum sodium lower than 110 experienced a rapid correction. An interesting point to highlight is that 58% of patients with ODS didn't have a rapid sodium correction rate, and almost 50%

of ODS population had initial serum potassium below 3.4 millimole per liter. This data showed that there might be another factor for developing ODS.

Bob Barrett: What are the key points and implications for hyponatremia patients and ODS?

Supawadee Suppadungsuk: That's a great question. First of all, the result from previous studies in both animals and humans have shown that rapid sodium correction is associated with osmotic demyelination. In this context, Dr. MacMillan's study also demonstrated that 42% of patients who developed ODS had treatment rate greater than 8 millimoles per liter per day. They also highlighted that 58% of the ODS patients didn't experience a rapid sodium correction. In these cases, the main change in sodium levels in the ODS patient was around 7 millimoles per liter per day. This finding is aligned with the largest study from Dr. Seethapathy and team, who studied 3,200 patients with hyponatremia. They found that five of seven, that was 70% of ODS cases, altered even without rapid sodium correction rate. This is very important because it suggests that rapid sodium correction might not be the only factor leading to ODS, as we know.

The main mechanism of ODS in hyponatremia is the change in serum osmolality, especially in brain cells that are adapted to a chronic hypo-osmolality environment. Under chronic, low osmolality conditions, brain cells adapt by releasing organic and inorganic osmolytes into the extracellular space to maintain osmotic balance after their adaptation. When these cells are suddenly exposed to a relatively hypertonic environment as a result of treatment, they reuptake these osmolytes, but not immediately. It happens at a slower rate than their release. This discrepancy can cause osmotic strain on brain cells, which lead to ODS.

Additionally, other electrolytes such as potassium and chloride might also be potential risk factor when corrected with an unclear mechanism. Hypokalemia was hypothesized that decreased sodium potassium ATPase activity in brain's vascular endothelial cells, which is affecting cell volume regulation, could be a potential link and also with chloride. Changes in chloride and sodium are often concordant. Even if the serum sodium correction rate is within the desired range, serum chloride can be rapidly corrected due to the use of chloride with fluids. The rapid change in chloride levels could potentially enhance neuronal osmotic stress and lead to a higher risk of ODS. Of course, these hypotheses need to be studied more carefully.

Bob Barrett: Well, finally doctor. What does this all mean for the management of hyponatremia and ODS? Can we define the

appropriate rate of correction of hyponatremia in clinical practice?

Supawadee Suppadungsuk: Thank you for your question. From a clinical perspective, we are always careful in treating and observing its complications. Previous evidence and data from Dr. MacMillan have shown that rapid sudden correction in hyponatremia is more common. Initial serum sodium lower than 110 millimole per liter was identified in most ODS patients who experienced rapid correction rates. Therefore, for patient with severe hyponatremia at baseline, or with other risk factors like hypokalemia, malnutrition, alcohol use, liver disease, or hypophosphatemia, it would be important to remain cautious with the treatment rate and closely monitor.

In contrast, patients without any risk factors for ODS, and with initial serum sodium above 120, may not require aggressive interventions after exposed to overly rapid sodium collection rate because they are at low risk on ODS. That's why the U.S. guideline recommend the sodium correction rate of 10 to 12 millimoles per liter per day for patients with a normal risk and 8 millimoles per liter for those at high risk. The European guidelines are also mentioned the correction rate at 10 millimoles per liter per day.

However, it's still challenging to determine the exact threshold at which ODS will not alter and prevent it, as both patient undergoing rapid and non-rapid sodium correction could develop ODS. Therefore, it is important to consider the patient's clinical context: cause of hyponatremia, duration of onset, and any significant concomitant risk factors, into getting all of these factor into decision making process, for the rate of sodium correction is essential for preventing ODS. Furthermore, including laboratory data, treatment records, and a clear definition of ODS diagnosis for further study are still needed. This comprehensive approach could help to clarify the appropriate rate sodium correction in hyponatremia patient in the future.

Bob Barrett: That was Dr. Supawadee Suppadungsuk from Mahidol University in Bangkok, Thailand. She is the lead author of a perspective article revisiting the rate of sodium correction in hyponatremic patients in the July 2024 issue of *Clinical Chemistry*, and she has been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.