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Review Article

Hyponatremia in Sick Children: A Marker of Critical Illness

Mir Mohammad Yusuf*

Assistant Professor, Critical Care Department, Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital, Bangladesh

***Corresponding Author:** Mir Mohammad Yusuf, Assistant Professor, Critical Care Department, Bangladesh Institute of Child Health (BICH), Dhaka Shishu (Children) Hospital, Bangladesh.

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Abstract

Children who required intensive care are vulnerable to electrolyte derangement and hyponatremia is the most common electrolyte abnormality among this population. Hence its implication is so much important with perfect interpretation. Abnormality of hyponatremia occurs in a variety of condition and results in morbidity or mortality; especially in acutely sick children indicate a poor prognosis. Moreover, a precise information on pathophysiologic implications and outcome of hyponatremia in sick children is lacking. In this review, we provide an update focused on the association between hyponatremia and critically sick hospitalized children and related concern.

Keywords: *Hyponatremia; Sick Children; Critical Illness*

Introduction

Abnormalities of sodium homeostasis are common electrolyte disorder encountered in sick children who need intensive care [1,2]. It has been reported that hyponatremia, occurring 3% to 30% among hospitalized patients [3-5]. Abnormality occurs in a variety of conditions and results in mortality and morbidity [3,6]. The causes of and treatments for hyponatremia can only be understood by having a grasp of the size of the body fluid compartments and sub-compartments and their regulation; how under normal circumstances the body is able to maintain the sodium concentration within a narrow range (homeostasis of body fluid osmolality); conditions can cause that feedback system to malfunction (pathophysiology) and the consequences of the malfunction of that system on the size and solute concentration of the fluid compartments [7].

Normal homeostasis

There is a hypothalamic-kidney feedback system which normally maintains the concentration of the serum sodium within a narrow range. This system operates as follows: in some of the cells of the hypothalamus, there are osmoreceptors which respond to an elevated serum sodium in body fluids by signaling the posterior pituitary gland to secrete antidiuretic hormone(ADH) (vasopresin) [8]. ADH then enters the bloodstream and signals the kidney to bring back sufficient solute-free water from the fluid in the kidney tubules to dilute the serum sodium back to normal, and this turns off the osmoreceptors in the hypothalamus. Also, thirst is stimulated [9]. Normally, when mild hyponatremia begins to occur, that is, the serum sodium begins to fall below 135 mEq/L, there is no secretion of ADH, and the kidney stops returning water to the body from the kidney tubule. Also, no thirst is experienced. This two act in concert to raise the serum sodium to the normal range [10-12].

Hyponatremia

Hyponatremia occurs 1) when the hypothalamic-kidney feedback loop is overwhelmed by increased fluid intake; 2) the feed-

back loop malfunctions such that ADH is always "turned on"; 3) the receptors in the kidney are always "open" regardless of there being no signal from ADH to be open; or 4) there is an increased ADH even though there is no normal stimulus (elevated serum sodium) for ADH to be increased.

Hyponatremia occurs in one of two ways: either the osmoreceptor-aquaporin feedback loop is overwhelmed, or it is interrupted. If it is interrupted, it is either related or not related to ADH [11]. If the feedback system is overwhelmed, this is water intoxication with maximally dilute urine and is caused by infantile water intoxication. "Impairment of urine diluting ability related to ADH" occurs in various situations: 1) arterial volume depletion, 2) hemodynamically-mediated, 3) congestive heart failure, 4) cirrhosis, 5) nephrosis, 6) Addison's disease and 7) syndrome of inappropriate antidiuretic hormone secretion (SIADH). If the feed-back system is normal, but an impairment of urine diluting ability unrelated to ADH occurs, this is 1) oliguric kidney failure, 2) tubular interstitial kidney disease, 3) diuretics or 4) nephrogenic syndrome of antidiuresis [11].

Sodium is the primary positively charged ion outside of the cell and cannot cross from the interstitial space into the cell. This is because charged sodium ions attract around them up to 25 water molecules, thereby creating a large polar structure too large to pass through the cell membrane: "channels" or "pumps" are required. Cell swelling also produces activation of volume-regulated anion channels which is related to the release of taurine and glutamate from astrocytes [13].

Symptoms

Hyponatremia is a common electrolyte disturbance occurring in critically ill patients [14]. Unusual weight gain and decrease urine output is the most important sign to predict hyponatremia clinically [15]. Symptoms range from nausea and malaise, with mild reduction in the serum sodium, to lethargy, decreased level of consciousness, headache, seizures and coma [16].

Classification

A blood test demonstrating a serum sodium less than 135mmol/L is diagnostic for hyponatremia [17]. Hyponatremia can be classified on the basis of serum osmolality, volume status and urinary sodium into hypertonic, isotonic and hypotonic types. Hypotonic hyponatremia is further classified into hypervolemic, euvolemic and hypovolemic as follows [18]:

- Hypovolemic hyponatremia: Decreased total body sodium and decreased total body water. The sodium deficit exceeding water deficit e.g. diarrhea.
- Euvolemic hyponatremia (dilutional): Normal body sodium with increase in total body water e.g. severe sepsis, severe perinatal asphyxia, pneumonia, meningitis, encephalitis.
- Hypervolemic hyponatremia(edematous): Increase in total body sodium with greater increase in total body water e.g. renal failure, cardiac failure, liver cirrhosis.

Sodium and its accompanying anions, chloride and bicarbonate, are the principal solutes in the extracellular fluid (ECF). They are the main determinant of ECF volume, since changes in its concentration cause changes in water intake and in renal water excretion, due to stimulation or suppression of thirst and antidiuretic hormone secretion, respectively. The ECF sodium concentration is normally held within narrow limits and the normal range is 135 - 145 mmol/l [19]. A low serum sodium concentration reflects either an excess of water or primary sodium depletion. Water retention may occur with an increased, normal, or reduced total body sodium content. Elucidation of the cause of hyponatraemia first requires consideration of the regulation of sodium and water balance in the newborn. After birth, extracellular fluid volume contracts, and this is accompanied by net negative sodium and water balance and weight loss. This period is of variable duration, but by the third or fourth postnatal day, sodium and water balance have become positive, and remain so until adult life [20]. Hyponatraemia is common in inpatients and this includes newborns in neonatal intensive care units. Surveys from around the world suggest that up to a third of very low birth weight infants are hyponatraemic in the first week after birth and between 25% and 65% thereafter [21]. It was found three times higher among the neonates with perinatal asphyxia and MAS. Most of the clinical symptoms were not significantly associated with hyponatremia. It was found two times and four times higher with neonates presented with unusual weight gain and decrease urine output respectively. Mortality was found three times higher among neonates who developed hyponatremia. Large number of neonate developed hyponatremia in ICU. Unusual weight gain and decrease urine output are the most important signs to predict hyponatremia clinically. Mortality was found

higher among neonates with hyponatremia. Prior to establishing a cause of hyponatremia, a detailed history should be obtained in order to exclude the numerous disorders capable of causing hyponatremia. Helpful historical details in identifying the responsible mechanism for hyponatremia include diet, fluid intake, gastrointestinal losses, amount of urinary output, and medications. Historical information can give important clues in deciding whether the hyponatremia is from an acute or chronic condition. This may help the physician in correlating the degree of hyponatremia with the patient's neurologic condition and influence the rate of sodium correction. Signs and symptoms of hyponatremia are primarily related to the dysfunction of the central nervous system and correlate with severity and rapidity of development of hyponatremia. These occur as osmotic fluid shifts result in cerebral edema and increased intracranial pressure. Whereas most patients with serum sodium concentration above 125 mEq/L are asymptomatic, those with lower levels typically have symptoms, especially in the setting of a rapid decrease. When sodium concentration drops below 105 mEq/L, life-threatening complications are likely to occur [3]. Symptoms generally occur only when hyponatremia is severe and may include vomiting, restlessness, irritability, hyporeflexia, seizure, coma, oliguria and weight gain [22-24]. Acute alterations in serum sodium concentrations contribute to neurological morbidity in sick neonates. Central pontine and extrapontine myelinolysis, regarded as the histopathological hallmark of hyponatraemia, has only occasionally been described in infants [5].

The presence of hyponatremia, its severity, and delay in initiating adequate treatment appear to be the main indicators for both morbidity and mortality. The fatality rate of patients with hyponatremia (when defined by a sodium concentration of < 130 mEq/L) is 60-fold compared to that of patients without documented hyponatremia. Morbidity and mortality rates are higher in hospitalized patients and those with acute onset or severe hyponatremia [25]. Serum Sodium were estimated by automated analyzer made by Dimention*RXL* MaxUSA [15].

Hyponatremia in critical illness

Hyponatremia in acutely ill children attending our pediatric emergency service was associated with a higher mortality and prolonged hospitalization. Although, the study did not aim at defining various factors which could have contributed to the higher mortality, several factors including the underlying cause, the severity of the illness, and the severity and the rate of development of hyponatremia could have contributed. Possibly the severity of illness itself could have determined the severity of hyponatremia too, as shown in our subsequent studies on children hospitalized for meningitis and pneumonia [26]. Findings of various authors [27-29] suggest that hyponatremia is an indicator of severe underlying disease and a pointer to poor prognosis.

Hyponatremia is also common in neonate in ICU and it is found 25% among very low birth weight neonate and common during first week of life [21]. In a study hyponatremia was present in 22.8% cases [15]. Hossain., *et al*. [30] found 16.6% hyponatremia in critically ill neonates in ICU. The reason for low incidence is that they excluded mild hyponatremia (serum sodium 130 - 135 mmol/l) cases from their study. The incidence of hyponatremia is unacceptably high in neonates in the ICU. This is attributable in large part to the administration of excessive amounts of water as hypotonic saline as maintenance fluid in situations in which ADH is secreted for non-osmotic reasons. Similar conclusion was drawn by Hoorn., *et al*. [31] from their study. The original guidelines for maintenance fluid may not be applicable in an era when the complexity and the severity of illness are seen. It puts neonates at risk for the development of adverse neurologic events and is largely preventable. The current teachings and practical guidelines for maintenance fluid infusions are based on caloric expenditure data in healthy children that were derived and published more than 50 years ago. A re-evaluation of these data and more recent recognition that hospitalized children are vulnerable to hyponatremia, with its resulting morbidity and mortality rates, suggest that changes in paediatrician, approach to fluid administration are necessary [32]. Perinatal asphyxia, neonatal sepsis and preterm low birth weight contributed majority of hyponatremia among very sick neonates but these diseases were found weakly associated with hyponatremia. Lane., *et al*. [33] and Modi., *et al*. [21] showed high incidence of hyponatremia among babies born after fetal distress and difficult deliveries. Hyponatremia was present in 5.2% among surgical cases. Bell., *et al*. [34] found 11% hyponatremia among surgical cases. Hyponatremia was found significantly high among the neonates who were less than 7 days of age. Modi., *et al*. [21] showed high prevalence of hyponatremia during 1st week of life. Hyponatremia was found significantly high among the sick neonates weighing > 2500g. Lambert., *et al*. [35] showed high occurrence of hyponatremia among low birth weight babies. Mean gestation was 36.83 ± 2.94 weeks in hyponatremia patients and 35.72 ± 3.51 weeks in neonates hav-

ing no hyponatremia. Modi., *et al*. [21] showed high incidence of hyponatremia in premature neonates. Hyponatremia often mimics the clinical manifestations of various disorders and is difficult to diagnose. Symptoms generally occur only when hyponatremia is severe [3,5]. Extracellular hypotonicity leads to intracellular oedema and severe symptoms may result from cerebral oedema [3]. Most of the clinical signs were weekly associated with hyponatremia but relative risk of development of hyponatremia among the neonates with unusual weight gain and decrease urine output were higher than that of not having those signs. Fluid retention due to inappropriate ADH secretion causes the weight gain and decrease urine output. Milionis., *et al*. [36] in their study found association between hyponatremia and weight gain. No relation was found between hyponatremia and hospital stay. But Sherlock., *et al*. [37] found increase length of hospital stay among the patients with hyponatremia. Mortality was found three times higher among neonates who developed hyponatremia. Different studies have found that hyponatraemia is associated with significant mortality [38,39].

Among hospitalized patients with hyponatremia, the reported mortality rate evolving over the course of more than 48 hours has varied between 10% and 27% (17) [40]. This is similar to mortality of 17% in severe hyponatremia [41]. Therefore, sick children needing emergency care and hospitalization have as high a risk of mortality as observed in adult patients.

Treatment of hyponatremia

The treatment of hyponatremia depends on the underlying cause [42], also depends on the duration of hyponatremia and volume status of the patients. How quickly treatment is required depends on a person's symptoms [42]:

Fluids are typically the cornerstone of initial management [42].

Sodium deficit = (140 - serum sodium) x total body water [43]

Total body water = kilograms of body weight x 0.6.

Fluids

Options include: Mild and asymptomatic hyponatremia is treated with adequate solute intake (including salt and protein) and fluid restriction starting at 500 ml per day of water with adjustments based on serum sodium levels. Long-term fluid restriction of 1,200 - 1,800 mL/day may maintain the person in a symptom free state [44].

Moderate and/or symptomatic hyponatremia is treated by raising the serum sodium level by 0.5 to 1 mmol per liter per hour for a total of 8 mmol per liter during the first day with the use of furosemide and replacing sodium and potassium losses with 0.9% saline.

Severe hyponatremia or severe symptoms (confusion, convulsions, or coma): Consider hypertonic saline (3%) 1 - 2 ml/kg IV in 3 - 4h. Hypertonic saline may lead to a rapid dilute diuresis and fall in the serum sodium. It should not be used in those with an expanded extracellular fluid volume.

There is serious neurologic sequel if hyponatremia is inappropriately treated [45]. Untreated hyponatremia may lead to cerebral swelling and its consequences because of hypotonicity [46].

Associated electrolyte abnormalities

In persons with hyponatremia due to low blood volume (hypovolemia) from diuretics with simultaneous low blood potassium levels, correction of the low potassium level can assist with correction of hyponatremia [47].

Precautions

Raising the serum sodium concentration too rapidly may cause pontine and extrapontine myelinolysis termed as osmotic demyelination syndrome [48-51]. It is recommended not to raise the serum sodium by more than 10 mEq/L/day [52].

Conclusion

Large number of sick children developed hyponatremia in Intensive Care Unit. Unusual weight gain and decrease urine output is the most important sign to predict hyponatremia clinically. Mortality was found higher among children with hyponatremia, hence it's a marker of critically sick hospitalized children especially in acute condition.

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