The Effect of Maintenance Fluid tonicity on Serum Sodium in Pediatric Patients

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ABSTRACT

Background: Hyponatremia is the most common electrolyte imbalance in clinical medicine. About 15% of hospitalized patients have hyponatremia. The type of administered intravenous fluid may lead to changes in serum sodium concentrations. Objectives: The aim of this study was to compare the effect of 1/3 2/3 fluid versus dextrose 5% half saline as intravenous maintenance fluid on serum sodium levels. Methods: In this cross sectional study, children aged 2 months to 12 years old admitted to the general pediatric ward of Bushehr Persian Gulf Shohada hospital were evaluated. They were randomly assigned to take 1/3 2/3 fluid (with 51 mEq/Lit sodium) or dextrose 5% half saline (with 77 mEq/Lit sodium). Serum sodium levels were checked before and 24 hours after the initiation of the IV fluid therapy. Results: A total of 295 patients were enrolled in this study and randomly received 1/3 2/3 fluid (N=152) or dextrose half saline (N=143). In children aged less than 5 years, there was a significant change in serum sodium levels after administration of 1/3 2/3 fluid (P=0.011 in <1 year old and P<0.001 in 1-5 year old). However, serum sodium was still in the normal range. This change was not significant in children above 5 years old. In children taking dextrose half saline, serum sodium levels did not change significantly (P=0.144). Conclusion: In a group of pediatric patients admitted to general pediatric ward, both 1/3 2/3 solution and dextrose 5% half saline are safe.

Key Words: *Hospital-acquired hyponatremia, Hyponatremia, Hypotonic solutions, Isotonic solutions, Maintenance fluid*

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INTRODUCTION

The average adult human body is 60% fluid (water and electrolytes). The two main fluid compartments are extracellular and intracellular, consisting one third and two thirds of the body fluid, respectively. The electrolytes are active components of body fluid and are divided into two groups: Cations including sodium, potassium, calcium, magnesium and hydrogen ions, and anions such as chloride, bicarbonate, phosphate, sulfate, and proteins. [1]

Hyponatremia is the most common electrolyte imbalance in clinical medicine. [1] About 30% of hospitalized patients have hyponatremia, defined as sodium levels of less than 135 mEq/Lit. [2]

Hyponatremia can lead to cerebral edema and intracranial hypertension due to influx of water into the brain parenchyma. [2] The pediatric brain is more susceptible to the impact of excess free water and the resultant hyponatremia than the adult brain. [3]

The occurrence of the electrolyte imbalance is often difficult to foretell because of the absence of specific early signs or symptoms, particularly in young children. [4]

Several conditions may result in hyponatremia by loss of sodium, excess of water, or both. In hospitalized patients,

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the type of administered intravenous fluid may also lead to changes in serum sodium concentrations. [1]

Isotonic fluids have a sodium concentration comparable with plasma (135-144 mEq/L). Plasma is about 93% aqueous and 7% anhydrous with a sodium concentration in the aqueous fluid phase of plasma of 154 mEq/L and osmolarity of 308 mosm/L, alike that of 0.9% sodium chloride (NaCl). Conversely, the sodium concentration of hypotonic fluid is lower than that of the aqueous phase of plasma. [5]

Virtually all hospitalized patients are at risk of developing hyponatremia due to the multiple potential stimuli for arginine vasopressin (AVP) production, such as hypovolemia (vomiting, diarrhea, diuretics, renal salt wasting, hypoaldosteronism), hypervolemia (nephrosis, cirrhosis, congestive heart failure, hypoalbuminemia), CNS disturbances (meningitis, encephalitis, stroke, brain tumor, etc.), pulmonary diseases (pneumonia, asthma, tuberculosis, etc.), cancers of lung, brain, CNS, etc., some medications, nausea, vomiting, pain, stress, postoperative state, and cortisol deficiency. [2]

Hypotonic fluids are still the parenteral fluid most commonly administered to pediatric hospitalized patients and their application is partly according to recommendations made by Holliday and Segar in 1957. [6] They reported the 4:2:1 rule for fluid management in the pediatric population (100 ml/100 kcal for the first 10 kg of body weight, 50 ml/100 kcal for 11–20 kg of body weight, and 20 ml/100 kcal for every kg of body weight beyond 20 kg), which was according to the principle that water requirements were associated with energy expenditure. They matched water needs with the concentrations of sodium (Na), potassium (K) and chloride (Cl) found in breast and cow's milk. They noticed that the Na requirements were 3 mEq/100 kcal/day and K requirements were 2 mEq/100 kcal/day leading to two different maintenance solutions: ¼ NS + 20 mEq/L of KCl and ½ NS + 20 mEq/L KCl. Both of these solutions are classified as hypotonic when compared to the tonicity of serum. [2, 6]

In the early 1980s, there were some case reports of death as a result of severe hyponatremia in patients receiving hypotonic fluids. [2, 7, 8]

With these concerns in mind, several researchers have argued that the utilization of hypotonic versus isotonic maintenance fluids in hospitalized pediatric patients has led to high incidence of hospital acquired hyponatremia. [9-22]

However, there are some arguments against the use of isotonic fluids, the most centered reason being the development of hyperchloremic metabolic acidosis. It may result in decreased myocardial contractility, hypoperfusion of end organs and complications such as acute kidney injury, coagulopathy and immune dysfunction. [23] Other possible harmful effects of these fluids may be hypernatremia, fluid overload, edema, and hypertension. [24]

Considering all the mentioned points, D5 1/2NS + 20mEq/L KCl –which is hypotonic- is recommended in the child who is NPO and does not have volume depletion or risk factors for nonosmotic ADH production. Children with volume depletion, baseline hyponatrmia, or at risk of nonosmotic ADH production should receive D5 NS + 20 mEq/L KCl, which is isotonic-. [1]

In this study, we evaluated the effect of type of the administered IV fluid on serum sodium levels and tested the hypothesis that hypotonic IV fluids may increase the risk of hyponatremia in hospitalized pediatric patients admitted in general pediatric ward. Since we have two different types of hypotonic fluids in our center, we compared the effects of these two different solutions with different sodium concentrations, on serum sodium levels.

METHODS

This cross sectional study was carried out in Persian Gulf Shohada hospital, Bushehr, Iran. The children between 2 months to twelve years old, admitted to the general pediatric ward who needed to take maintenance intravenous fluid were studied. The patients with the following conditions were excluded from the beginning: cardiovascular disease, renal disease, CNS problems, thyroid disease, and any patient in shock state or with abnormalities in serum sodium levels. After admission, 2 ml blood sample for evaluating serum sodium and other essential lab tests was obtained from each patient. Patients with abnormality in blood levels of sodium (less than 135 and more than 145 mEq/Lit) or other electrolyte imbalances were excluded from the study. Informed consent was taken from all the patients' parents or guardians. This study was performed with the approval of the ethics committee of Bushehr University of Medical Sciences. The study was done in accordance with the Declaration of Helsinki.

The study was performed during a 6-month period. The monthly average of the patients admitted to our center was 416. A total number of 295 patients were enrolled in this study, 152 of them taking 1/3 2/3 and 143 receiving D5 1/2NS fluid. The maintenance fluids we used were 1/3 2/3 (one third of which is NS and the remaining consists of D5, thus containing 51 mEq/Lit sodium) and Dextrose half saline with 77 mEq/Lit sodium concentration. After admission and before starting IV fluid, 2 ml of blood sample for evaluating sodium and other essential lab tests was obtained from each patient. Then, intravenous maintenance fluid was started with the following method: On even days of the week (Saturday, Monday and

Wednesday), 1/3 2/3 serum was used, whereas on odd days (Sunday, Tuesday and Thursday), Dextrose half saline was administered. On Fridays, the mentioned fluids were used interchangeably every other week. Twenty four hours following the initiation of fluid, 2 ml of blood sample was taken and sent to the laboratory. After centrifugation (10 minutes, 3500rpm), sample serum was isolated and sodium level was measured with ISE electrolyte analyzer JOKOH (Japan).

This table shows the variables in our study.

	Variable	Type of variable		Quantitative		Qualitative		Measurement	Units
		Dependent	Independent	Continuous	Discrete	Nominal	Ordinal		
1	age	*					*	According to patient records	years
2	Serum sodium level		*	*				According to patient records	mEq/Lit
3	Type of received IV fluid		*			*		According to patient records	

RESULTS

The mean serum sodium concentrations before and after receiving 1/3 2/3 IV fluid were 136.2 mEq/Lit (SD=1.93 mEq/Lit) and 137.18 mEq/Lit (SD=1.71 mEq/Lit), respectively. There was a significant difference between serum sodium levels before and after administration of this hypotonic fluid (P<0.001).

However, the effect of IV fluid therapy with 1/3 2/3 solution on serum sodium level was different according to the patient's age. In all age groups, there was an increase in serum sodium concentration after receiving hypotonic fluid. However, only in children under 5 years old, this difference is statistically significant (P=0.011 for <1 year old and P<0.001 for 1-5 year old patients).

In children taking D5 half saline, the mean serum sodium concentration was 136.5 mEq/Lit (SD=1.93 mEq/Lit) before and 136.3 mEq/Lit (SD=1.71 mEq/Lit) after receiving the fluid. The difference between sodium levels was not significant (P=0.144).

DISCUSSION

None of our patients developed hyponatremia after taking any of the two types of hypotonic IV fluids. To our surprise, in a group of patients aged less than 5 years old, serum sodium levels even increased after administration of 1/3 2/3 fluid. Despite this rise, which was statistically significant, the sodium levels were still in the normal range. In the other group of patients who were taking dextrose half saline as maintenance IV fluid, no significant changes were observed in serum sodium levels.

Since 1957, hypotonic solutions were the choice IV maintenance fluids in pediatric patients according to Holliday and Segar's landmark paper. [6] However, in the last decades several studies have questioned the safety of this approach and argued that isotonic solutions should be the standard of care in hospitalized children.

Most of the previous studies have demonstrated that hyponatremia is more common in patients receiving hypotonic fluids. [9-22]

According to a systematic review by Choong K., et al in 2006, there is some evidence that hypotonic solutions may have a potential harm, and isotonic or near-isotonic solutions may be more physiologic and a safer choice in children who are acutely ill or in the perioperative period. However, they stated that most of the reviewed studies were poorly and differently designed. They were heterogeneous in design, small, of variable quality, did not allow for confounding factors, and focused on a limited pediatric population. [25] Another systematic review by Beck CE. in 2007 also stated that for the same reasons, further evidence is required to find the appropriate maintenance solution for hospitalized children. [26]

In a Cochrane systematic review by McNab S., et al in 2014, [9] randomized controlled trials that evaluated isotonic versus hypotonic intravenous fluids for maintenance IV fluid in 1106 children. Isotonic intravenous maintenance fluids were shown to decrease the risk of hyponatremia when compared with hypotonic intravenous fluids. They reported that the results apply for the first 24 hours of administration in a wide group of primarily surgical pediatric patients with varying severities of illness. [9]

Three meta analyses, carried out in 2014 and 2015, were also in concordance with the hypothesis that there is an elevated risk of hyponatremia in children administered hypotonic fluids. [20-22]

One study performed by Valadao MC, et al. in 2007 compared hypotonic versus isotonic solutions as maintenance IV fluid in children in postoperative appendectomy period in a randomized controlled trial. They noticed that the use of hypotonic solution did not increase the risk of hyponatremia when compared to isotonic saline, and children who received hypotonic

solution showed greater cumulative fluid balance in the preoperative period. [27]

In the study by Saba TG, et al. in 2011, the rates of change in serum sodium for patients administered either hypotonic or isotonic IV fluids for maintenance needs were compared in a randomized controlled trial. They evaluated 37 children, 16 taking isotonic and the remaining 21 receiving hypotonic fluid. Based on the results, when administered at the proper maintenance rate and accompanied by adequate volume expansion with isotonic fluids, 0.45% saline did not lead to a drop in serum sodium during the first 12 hours of fluid therapy in children without severe baseline hyponatremia. They suggested that their findings should be confirmed in a larger study. [28]

Most of the above studies did not separate the critically ill and postoperative patients from those who are in general ward. In the study performed by Friedman JN, et al. published in 2015, only patients admitted in general pediatric ward were included. In this double-blind randomized clinical trial, 110 children with normal baseline serum sodium levels who were anticipated to require intravenous maintenance fluids for 48 hours or longer were investigated. Children that required specific fluid tonicity and volumes were excluded. The primary result was defined as mean serum sodium level at 48 hours. The secondary outcomes were mean sodium level at 24 hours, hyponatremia and hypernatremia, weight gain, hypertension, and edema. Fifty four patients received isotonic fluids and 56 received hypotonic fluids. They found no clinically significant difference in the primary outcome of mean serum sodium level at 48 hours after IV fluid administration. There were, however, 2 cases of hyponatremia in the hypotonic group at 24 hours. The study concluded that isotonic maintenance fluid administration is safe in general pediatric patients and may result in fewer cases of hyponatremia. [29]

In the last edition of Nelson textbook of pediatrics, D5 1/2NS + 20mEq/L KCl –a hypotonic fluid- is recommended in the child who is NPO and does not have volume depletion or risk factors for nonosmotic ADH production. Children with volume depletion, baseline hyponatrmia, or at risk for nonosmotic ADH production should receive D5 NS + 20 mEq/L KCl –an isotonic fluid-. Surgical patients typically receive isotonic fluids (NS, LR) during surgery and in the recovery room for 6-8 hours postoperatively. Subsequent maintenance fluids should be D5 NS or LR, with addition of 10-20 mEq/L of KCl based on the serum potassium and the clinical setting. [1]

In this study, we aimed to focus on pediatric patients admitted to general pediatric ward. We did not include the critically ill ICU patients or patients who had undergone a surgical procedure in our study. So we administered two different types of hypotonic fluid and evaluated their effect on serum sodium levels.

As we know, it is believed that the etiology of hyponatremia in hospitalized patients is antidiuretic hormone (ADH) secretion in response to stress. Hypovolemia (e.g. vomiting, diarrhea, blood loss), hypervolemia (e.g. cirrhosis, congestive heart failure, hypoalbuminemia), central nervous system dysfunction (e.g. head injury, meningitis, hypoxia), pulmonary disease (e.g. pneumonia, asthma, bronchiolitis, acute respiratory failure), malignancy, and other stressors (e.g. nausea, pain) are among the most common causes of ADH secretion. [2] It is possible that the lower rate of hyponatremia in our study is attributed to the fewer factors leading to excretion of ADH in them, since all patients with critical problems such as CNS problems, heart or kidney disease, hypovolemia or any abnormalities in serum sodium levels were excluded from the study in the first step.

CONCLUSION

According to our results, in a group of pediatric patients admitted to general pediatric ward, there is no significant decrease in serum sodium levels after receiving hypotonic fluids containing either 51 mEq/L or 77 mEq/L sodium. Therefore, at least in children who are not critically ill or in the perioperative period, both these hypotonic solutions are still safe to be administered.

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