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Comparison of Two Intravenous Fluid Maintenance Therapy with Different Sodium Concentrations in Hospitalized Children: A Randomized Trial Study

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Introduction: Hyponatremia refers to the serum sodium levels less than 135 mEq/L, which can even lead to death. Accordingly, the present study compared the effects of intravenous fluid maintenance treatment with different concentration levels of sodium.
Materials and Methods: In an investigative study to evaluate children admitted to the Pediatric Intensive Care Unit (PICU) of Bahrami Children's Hospital (2012-2013) which required intravenous fluid therapy and aged one to 14 years were evaluated. They were randomly divided into two groups: fluid treatment with 50 mEq/L (group I) and 100 mEq/L (group II) sodium concentrations. The fluids were calculated according to Holliday-Segar formula. Sodium of plasma [P (Na)] and Urine specific gravity (USG) were measured at the time of admittance (first P (Na) and USG) and 24 hrs after treatment (second P (Na) and USG).
Results: 108 children were admitted into the study. Significant differences were noted in the second P (Na) levels and differing of first and second P (Na) ($P<0.008$ and $P<0.011$). In the first group, 14 cases and in second three cases were hyponatremia (P (Na) < 135 mmol/L), but they weren't symptomatic during the study. The difference between first and second USG was greater in group I ($P <0.023$).
Conclusions: There was relation between the sodium of the IV fluid and decreased P (Na) concentration in the children who were undergoing intravenous (IV) fluid therapy. There were no Symptomatic hyponatremia cases reported, due to the decrease of P (Na), nor in the 24 hours following the IV therapy treatment.

Keywords: Fluid Therapy; Specific Gravity; Sodium; Hyponatremia

Running Title: Fluid maintenance therapy with two different concentrations of sodium in hospitalized children

Introduction

The purpose of intravenous (IV) therapy is the replacement of water and mineral of the body fluids in patients who could not maintain hydration orally. The combination of rehydration in pediatric patients has not yet been determined accurately yet [1].
According to the conventional methods, IV fluids in children, this therapy was based on a recommendation made in 1957 by Holliday and Segar [2-3]. More recent studies have shown that the hyponatremia incidence in hospitalized children increased following the use of this formula, the side effects were serious complications and even death [4-6].
Hyponatremia (a sudden drop of sodium concentration levels) refers to the serum sodium levels less than 135 mEq/ L, due to an excess of

water in relation to sodium in the extracellular fluid. The symptoms and signs of severe hyponatremia are nausea, vomiting, lethargy, impairment of orientation, loss of tendon reflexes, convulsions, and death due to cerebral edema and herniation [7]. This is due to the fact that children much more intracellular fluid volume and are susceptible to cerebral complications due to hyponatremia [8].

In recent studies, it was demonstrated that the use of hypotonic fluid can cause hyponatremia, and in some cases can become symptomatic. In several studies showed that there were a number of cases with pediatric mortality following the use of a hypotonic solution [6, 9-10] and the use of hypotonic solutions in hospitalized children can increase the risk of hyponatremia by 30% [11-13]. Nearly all children who are in need of IV maintenance fluid therapy are at the risk of Antidiuretic Hormone (ADH) increased secretion [9-10]. In addition, children are at risk of seizures due to hyponatremia, but the seizure threshold in children is lower than adults in hyponatremia, this could be due to the greater volume of the brain in children [2, 6, 9-10].

In hyponatremia, there are a true hypo-osmolar state and in the hyponatremic patient, the plasma sodium levels (P (Na)) measurement is the initial approach [14-15]. The next step after confirming the hypo-osmolar state is the determination of the kidneys ability to dilute the intact urine by measuring urine specific gravity (USG) [16]. This problem can be noted more in children with specific conditions. According to the significance of this issue in hospitalized children, the present study was designed to compare the effects of intravenous fluid therapy with different concentrations of sodium, on the plasma sodium levels in patients admitted to the pediatric intensive care unit (PICU) of Bahrami Children's Hospital (2012-2013).

Materials and Methods

This study was an investigative examination of the IV fluid therapy in the Pediatric Intensive Care Unit (PICU) of the Bahrami Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran (2012 to 2013). The pediatric patient's observed in this study were one to 14 years of age. The IV therapy in question, was administered for a minimum period of 24 hours, and evaluated. The data collection was performed via an interview with the admitting physician as well as the admission records of the patient.

This study was performed according to the principles of the Helsinki Declaration. The consent forms were obtained from the parents of all patients involved, and all benefits and harmful potentials of the research were explained. Cases were unsatisfactory according to this study's theory and with the lack of discretion of the parents, excluded from the study. The children in the study were evaluated by a physician for any possible risks of complications daily and for 48 hours upon release from the hospital. All tests were performed in Bahrami hospital lab. The blood samples were collected and sodium level of the plasma was measured by Perkin Elmer Flame Photometer (model 52A). The Schuco Clinical Refractometer (model 5711-2021) was used for USG measurement.

The first specimen for analysis of P (Na) and USG were collected at the time of admission (first P (Na) and USG) and a second specimen collated 24 hrs following the initial IV treatment (second P (Na) and USG). In all cases, the data collected was double checked for accuracy and to verify the results of the laboratory tests prior to recording the data in the appropriate form and in a timely manner. In both age groups in which hyponatremia cases were reported, all symptoms and complications were evaluated and recorded. In this study, 120 patients, aged one to 14 years and admitted to the PICU, were evaluated. Twelve patients for various reasons were excluded and 108 children were admitted to the study. The children were divided into two groups based on the randomization principles. A randomized list of patients was prepared for each group and intervention was as follows: Children were randomly assigned to two groups of 50 mEq/L (group I, N=53) and 100 mEq/L (group II, N=46) sodium concentration and received these IV fluids for 24 hours. Twenty two males and 24 female patients were in the first group and 33 male and 22 female patients were in the second group.

The following patients were excluded from the study: diagnosed at risk for cerebral edema, diabetic ketoacidosis, with acute or chronic renal parenchymal issues, cerebral trauma's, heart disease, hypoglycemia, abnormal ADH secretion, diabetes, pituitary or hypothalamic disorders, patients with post-operative blood loss, cranial and thoracic surgery, cirrhotic patients, severe malnutrition, and patients receiving IV therapy not designed for this study (exclusion criteria).

Additionally, children with plasma levels of sodium lower than the normal range (135-145 mmol/L) which required cardiopulmonary

resuscitation, intubation, early oral nutrition, decision to change fluid therapy and death were also excluded (withdrawal criteria).

Sample size calculations: The average of declining plasma sodium levels following the initial 24 hours IV fluid therapy was considered a major consequence. According to the results in previous studies, the sodium loss in fluid therapies was 1.7-3.7 mmol /L and in isotonic fluids the sodium levels were 0.8 mmol/L. The number of patients in each group was at least 50 patients.

Data analysis: The data were analyzed using the SPSS software. For comparison of two groups, chi-Square and t-test was used. P. Value of 0.05 and study power of 80% was assumed.

Results

The mean age of in all patients was 54.27±41.23 months. The mean age of first group was, 47.08±37.55 months and in the second group was 59.55±44.23 months and there was no significant difference in the age between two groups (P< 0.121). The mean weight of the children was 16.19±7.2 kg. It was 15.55±7.74 kg in the first group and 16.4±6.7 kg in the second group. There weren't any significant differences in the weight of patients in the two groups (P < 0.992).

In this case study, of the diagnosis and cause for hospitalization of the children were separated into seven major groups (respiratory disease, Sepsis, gastrointestinal diseases, poisoning, gastroenteritis, meningitis and other items). The maximum number of patients (60 patients) was in the group of respiratory diseases. The remaining patient diagnosis and cause of patient's hospitalization were as follow: four patients with Sepsis, four patients with gastrointestinal diseases, 11 with toxicity, 16 with diarrhea and vomiting, six with meningitis and seven patients with other items disease. The mean of the first P (Na) levels in the collected specimens in all patients was 139.95±5.08 mmol/L. The mean of the first P (Na) in the first and second groups was measured and there were no significant differences observed in the mean plasma sodium in the two groups (P < 0.847, table 1).

The mean of the second P (Na) in the collected specimens was 138.17±5.86 mmol/L. According to table 1, the mean of the second P (Na) specimen in the first and second group specimens in all patients was recorded. There were significant differences in the second P (Na) in patients of two groups (P < 0.008, table 1). In all patients, the mean of the first and second P (Na) difference was 1.67±6.96 mmol/L. The mean differences in the first and second groups were recorded in table 1. The significant difference was observed between the two groups in this factor (P < 0.01, table 1).

Table 1. The comparison of factors mean in study groups [fluid treatment of 50 mEq/L (group I) and 100 mEq/L (group II) sodium concentrations] in Children aged 1- 14 years

Factors	Groups	Mean±SD	P-value
Age (month)	Group I	47.08±37.55	0.121
	Group II	59.55±44.23	
Weight (Kg)	Group I	15.55±7.74	0.992
	Group II	16.4±6.7	
First P(Na)(mmol/L)	Group I	140.34±7.74	0.847
	Group II	139.71±3.19	
Second P(Na)(mmol/L)	Group I	136.5±6.14	0.008
	Group II	139.6±5.28	
Difference of first and second P(Na)(mmol/L)	Group I	3.52±7.26	0.011
	Group II	0.00±6.27	
First USG	Group I	1016.72 ± 8.03	0.989
	Group II	1017.21 ± 8.03	
Second USG	Group I	1012.02±6.86	0.6
	Group II	1012.02±5.82	
Difference of first and second USG	Group I	4.26±10.19	0.023
	Group II	4.12±9.65	

Totally, hyponatremia (P (Na) <135 mmol/L) cases were 21 and nine cases of hypernatremia (P (Na) >145 mmol/L).

In the first group, the reported number of hyponatremia cases was 14 and the diagnosed positive hypernatremia cases were three. In the second group, hyponatremia cases reported were seven and diagnosed positive for hypernatremia cases were six. There was no significant difference in the frequency of the patient whit hyponatremia in two groups (P<0.067). The mean of first USG in the all cases was 1016.96 ± 8.14. According to the table 1, USG in the first and second groups were recorded. There was no significant difference in the first USG in two groups (P < 0.989, table 1).

Totally, the mean of the second USG in the all cases was 1012.6±6.32. The second USG in the first and second groups were recorded in table 1 and there was no significant difference in the first USG in two groups. There was no significant difference in the first USG in two groups (P<0.6).

In all patients, the mean of the first and second USG difference was 4.08 ± 9.95. In the first and second groups, this factor was measured (table 1), there was significant difference in two groups (P<0.023).

Discussion

In the present study, two types of IV fluid therapy for hydration maintenance in children were used, included fluids with 50mEq/L and 100 mEq/L Na concentrations. According to the results, the sodium concentration in 48 hrs decreased significantly, in this sampling there were no abnormalities associated with the plasma levels of Na in these patients.

Over the past half century, the daily pediatric sodium therapy was based on recommendations made in 1957 by Holliday and Segar. The amount of Na has been estimated 3 mmol per 100 ml of maintenance fluid [2]. However, clinical studies have not recommended its use as a maintenance fluid therapy; the hypotonic fluids were used widely in the treatment of children [17]. According to the studies, the mortality rate due to iatrogenic hyponatremia raised questions regarding the safety of the proposed Holiday-Segar method for use of the therapeutic hypotonic fluids in children [4-6]. Whether the use of therapeutic isotonic fluids is appropriate in hospitalized children will be discussed further in this study. Arieff et al. (1992) reported that from 24,412 children with consecutive surgical admissions, the death rate of hyponatremia was 8.4%, which demonstrated a hazard in the clinical value of hypotonic fluid therapy [9].

The mean of the P (Na) in the first collected specimen and second specimen collected 24 hours following fluid therapy were evaluated. The mean of the first P (Na) was similar in both groups. However, the second P (Na) was lower in the first group. According to the results, patients treated by fluid with lesser Na concentration, were more at the risk of hyponatremia. However, the decreased levels of Na in the plasma are not associated to the fluid volume and are in relation to the Na concentration in the fluid of treatment [18].

Choong et al (2011), studied two patient groups of patients 6 months to 16 years of age post-operatively, who received a 24 hrs treatment of an isotonic (*N* = 128) and hypotonic (*N* = 130) IV fluid therapy. The results demonstrated that the risk of hyponatremia in patients treated by hypotonic fluid was higher than that of the isotonic group [19]. Also, Wang et al. (2014) conducted a meta-analysis and showed that plasma sodium levels dropped in children received hypotonic fluid [20]. The hypotonic IV fluid is introduced as the primary source of free fluid [21-22].

However, in a study on the effect of hypotonic and isotonic fluid conducted by Mathur et al. (2009) there were no significant differences noted in the use of these fluids for hyponatremia [23].

Montanana et al. (2008) recorded no difference in the blood electrolyte concentration 24 hrs after hypotonic and isotonic fluid treatments .The plasma sodium loss in the first group was more than the second group. Yung et al. (2009) in their study of the fifty patients (37 surgical) showed that both groups had a drop in their blood plasma levels, and demonstrated that the plasma sodium losses in the group with dextrose saline were more than the normal saline group [22].

There were no differences noted in the frequency of hyponatremia cases in either of the two groups of study. Despite the fact, that there were no cases with symptomatic hyponatremia diagnosed during the study. Hoorn et al. (2004) evaluated 1586 children 48 hrs after fluid therapy referred to the hospital emergency. The results showed 131 patients with hyponatremia (P (Na) <136 mmol/L). Ninety six patients were enrolled in the study and were determined that 40 cases had hospital hyponatremia.

Accordingly, they suggested the use of an isotonic fluid in the treatment of children with P (Na) <138 mmol/L at the time of admission [11]. Montanana et al. (2008) in their study on the one hundred twenty–two pediatric patients hospitalized in the intensive care unit showed that 20.6% of patients receiving hypotonic fluid and 5.1% of the cases receiving isotonic fluid became hyponatremia after 24 hrs and there were statistical significances in the two groups [24]. Kannan et al. (2010) studied the effects of IV fluids (A: receiving 0.9% saline fluid, B: 0.18% Saline and C: 0.18% Saline with calculated volume by Holliday-Segar formula) on the serum sodium levels, 167children aged three months to 12 years. In this study, Group A was eight times less than Group B and patients in group B was four times less than in group C at the risk of hyponatremia [25]. This study confirmed the hyponatremia was due to the hypotonic fluids. Wang et al. (2014) in their meta-analysis showed that treatment with hypotonic fluid increase the risk of hyponatremia and severe hyponatremia [20].

Although, in several studies symptomatic

hyponatremia with seizures [26], nausea and vomiting [11] and even death in some cases [9] have been reported, however in the present study the symptomatic hyponatremia weren't observed, despite the most of the patients were with respiratory disease

The USG at the time of admission and 24 hrs after the IV fluid treatment was similar in both groups. The differences of first and second USG in the first group were more elevated. Montanana et al. (2008) in their study showed that there were patients with hyponatremia in the group receiving hypotonic fluid; however the USG levels were similar in isotonic and hypotonic fluid groups [24]. Based on the obtained results, it can be stated that the use of isotonic fluids can prevent complications of hypotonic fluids and is a better option in patients at risk for hyponatremia. Moritz et al. (2007) in their review article demonstrated that the use of 0.9% saline fluid could prevent hyponatremia due to the IV transfusion and suggested the use of isotonic fluids for the pediatric cases, menopausal women, post-op patients, patients with cerebral injuries, infectious disease, lung disease and hypoxia [10].

Conclusions

It can be concluded that the amount of sodium in the maintenance IV fluid therapy can affect the plasma level of Na, and in the fluid with 50mEq/L Na concentrations the plasma sodium losses are greater. However, in this study no symptomatic hyponatremia cases were reported.

Conflict of Interest

All authors had no conflict of interest

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