Effect of Isotonic and Hypotonic Fluid Therapy on Serum Sodium: A Randomized Controlled Trial

Moslem Sedaghattalab[1], Soheila Khajezadeh[1], Akvan Paymard[1], Parisa Mansouri[1], Rozina Abbasi Larki[2], Leila Manzouri[3]

[1] *Department of Internal Medicine, School of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran*

[2] *Department of Nephrology, School of Medicine, Yasuj University of Medical Sciences, Yasuj, Iran*

[3] *Department of Community Medicine, Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran*

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Abstract- There is little consensus about the type of maintenance fluid therapy and it's the effect on serum sodium in adults. Thus, this study was conducted to assess the effect of maintenance fluid therapy on serum sodium of hospitalized patients in the intensive care unit. This randomized clinical trial was carried out on 64 patients aged 18-90 years hospitalized in the intensive care unit (ICU) of Imam Sadjad and Shahid Beheshti hospitals, Yasuj, Iran, in 2017. These patients were randomly allocated to take 2500-3000 milliliters of intravenous maintenance isotonic (0.9% saline) or hypotonic (0.45% saline) fluids daily. Blood and urine samples were taken to measure biochemical parameters before and 48 hours after the intervention. Data analyses were done by using SPSS 16 software via descriptive and analytic statistics. Twenty-eight patients in the 0.9% saline group (19 male and 9 female) and 32 patients in 0.45% saline (20 male and 12 female) completed the study. There was no significant difference between two groups in sodium (*P*=0.94), potassium (*P*=0.21), sugar (*P*=0.91), creatinine (*P*=0.21), Blood Urea Nitrogen (*P*=0.99), systolic (*P*=0.81) and diastolic (*P*=0.73) blood pressure, PH (*P*=0.27), bicarbonate (*P*=0.8), and urine specific gravity (*P*=0.73). Based on the results of this study, it was shown that the administration of maintenance hypotonic fluids has been appropriate for the patients and will not face them with the risk of hyponatremia.

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Introduction

The critical aspect in caring the critically ill patient is the administration of intravenous fluid therapy, which is given in the form of bolus infusion for resuscitation or as a continuous infusion, in situations in which the patient is not able to eat orally. The main goal of intravenous fluid therapy is to maintain the balance between the extracellular volume and electrolytes. Thus, the most proper fluid therapy is one that is able to provide both water and electrolyte to supply blood for tissues without causing any complication arising from an increase or reduction in the volume of fluid and electrolytes (1).

In terms of the concentrations of sodium plus potassium, intravenous fluids are divided into two types of isotonic (almost equal to the plasma's sodium concentration of plasma sodium) and hypotonic (less than the plasma's sodium concentration). Since the dextrose included in intravenous fluids has no effect on tonicity, and it is rapidly metabolized and taken via tissues (1), the sugar included in fluids is not calculated.

The human body is able to maintain its water content and plasma's osmolality in the normal range in spite of retrieving the vast amount of water and electrolytes (2). The balance between water and sodium content is controlled through a system called Renin Angiotensin Aldosterone System (RAAS) - Natriuretic peptide-Arginine vasopressin (AVP). Plasma's osmolality is regulated via thirsty mechanism and free water clearance. In patients who are unable to tolerate fluids orally, plasma's osmolality is initially controlled through AVP secretion and determining the amount of free water clearance (3).

Any condition can cause an increase in AVP secretion or disruption in AVP activity and may make a change in plasma's sodium concentration. There are some

Corresponding Author: L. Manzouri
Department of Community Medicine, Social Determinants of Health Research Center, Yasuj University of Medical Sciences, Yasuj, Iran
Tel: +98 9131867975, Fax: +98 7433337219, E-mail address: manzourileila@gmail.com

hemodynamic and non-hemodynamic drivers in critically ill hospitalized patients, which can lead to an increase in AVP secretion and face them with the threat of hyponatremia. Hemodynamic drivers include hypovolemia, hypotension, any condition accompanied by edema (such as heart failure, cirrhosis, nephrotic syndrome), and sepsis (4). Non-hemodynamic drivers include pain, vomiting, nausea, hypocalcemia, hypercapnia, hypoglycemia, and conditions during surgery (3).

Different studies have shown that administration of hypotonic fluids in children has been accompanied by the high incidence of hospital-acquired hyponatremia, and there have been more than 100 reported cases of iatrogenic deaths or stable neurological deficits relating to hyponatremic encephalopathy (5).

Hyponatremia, which includes less than 135 mmol/l plasma's sodium concentration, is the most common electrolyte imbalance in hospitalized patients. About 15-30% of hospitalized children and adults become complicated with this disorder (6).

The most frequent complication caused by hospital-acquired hyponatremia is hyponatremic encephalopathy, which is an emergency medical condition, can be mortal, and, if not treated, will cause irreversible brain damages (7).

Prevention of hospital-acquired hyponatremic encephalopathy is very critical and essential and can progress from some non-specific symptoms to extremely extensive stages. Most of these symptoms include headache, nausea, vomiting, and general weakness. Advanced symptoms include seizure, apnea, non-cardiac pulmonary edema, and neurological symptoms (8).

In spite of the extensive need for intravenous fluids in critically ill patients, there is little consensus about the administration of the most proper amount of fluid, and there is an enormous difference between the composition of intravenous fluids and their clinical application methods. In the clinical setting, hypotonic fluids are often used in both children and adults, which are associated with a high incidence of hospital-acquired hyponatremia, and so far, hundreds of deaths and permanent neurological deficits relating to hyponatremic encephalopathy have been reported (1).

It should be mentioned that most of the studies about fluid therapy have been carried out on children, and there are very limited documentations about adults; and most of the recommendations about fluid therapy have been based on medical history and opinions, which necessitates more studies (1). Thus, this study has been conducted on adults and has studied the effect of maintenance fluid therapy on hospital-acquired hyponatremia in patients hospitalized in the intensive care unit (ICU).

Materials and Methods

In this randomized clinical trial study, 64 hospitalized patients in the ICU of Yasuj Imam Sadjad and Shahid Beheshti hospitals that met inclusion criteria were included. These patients were randomly allocated to take maintenance isotonic (0.9% saline) or hypotonic (0.45% saline) fluids.

The inclusion criteria were as follow age ≥18 years, stable vital sign, no contraindication to taking hypotonic and isotonic fluids, absence of electrolyte imbalance, brain lesions (tumor, ischemia, and hemorrhage), chronic renal failure, chronic heart failure, hypertension, edema, adrenal insufficiency, acute or chronic neurological disorders and being NPO. Also, patients on diuretics and sodium bicarbonate for drug intoxication or rhabdomyolysis were not included, too.

After taking written informed consent from patients or their companions, the patients entered into the study. The patients did not bear any extra cost or blood sampling because considered biochemical parameters were tested as routine daily or twice a day in ICU.

During the study, patients were monitored frequently, and if any instability in vital signs or tests occurred, the patient was excluded and treated. This study had been confirmed by the ethics committee of Yasuj University of Medical Sciences (ethic code YUMS.REC.1394.70).

Before starting the intervention, blood and urine samples were taken to measure sodium, potassium, sugar, creatinine, Blood Urea Nitrogen, and urine specific gravity. Systolic and diastolic blood pressure was recorded, and arterial blood gas was done, too.

Afterward, based on sequential, random allocation (ratio of 1.1), patients were allocated to two groups. One of these groups received maintenance 0.9% saline, and the other received 0.45% saline. Both groups received 2500-3000 milliliter intravenous fluids daily. 50% dextrose was added to the above-mentioned fluids. All tests were repeated 48 hours after the initiation of intravenous fluid therapy. During the study, the patients were regularly monitored in terms of vital signs (blood pressure, heart rate, and body temperature), urinary output, and serum electrolytes.

A sample size of 64 patients was calculated using comparing two mean formulas. It was estimated to yield 80%power (type II or beta error of 0.20%) and type I error of 0.05 (μ_1=136= Mean of sodium in the hypotonic group,

μ_2= 138= Mean of sodium in the isotonic group, S_1=2.1= S.D. of sodium in the hypotonic group, S_2=1.9= S.D. of sodium in the isotonic group) (9).

Statistical analysis

Data analyses were performed by using $SPSS_{20}$ (SPSS, Chicago, IL, USA) software. Continuous variables with normal distribution were presented as mean± standard deviation and were compared by independent samples *t*-test and paired *t*-test. If the variables didn't follow the normal distribution, a non-parametric test (Mann-Whitney) was used. Nominal variables were taken as counts (or frequencies) and were compared by the *Chi*-square test. All statistical tests were based on two-tailed probability. $P<0.05$ was considered statistically significant.

This trial was registered in the Iranian Registry of Clinical Trial (www.irct.ir) with the registration number of ID: IRCT2017101522869N5

Results

In this clinical trial study, 64 hospitalized patients in ICU were randomly allocated to two groups (32 per group). In the 0.9% saline group, four patients were excluded from the study (3 due to discontent and another one due to hyponatremia 24 hours after initiation of intravenous fluid therapy). Finally, 28 patients in the 0.9% saline group (19 male and 9 female) and 32 patients in 0.45% saline (20 male and 12 female) completed the study (Figure 1).

The demographic and biochemical characteristics of participants are presented in Table 1.

A comparison of the biochemical parameters after the intervention is shown in Table 2.

Given the statistically significant difference in basic creatinine level in two groups and its effect on sodium, potassium, creatinine, its effect was controlled as a confounding factor using the General Linear Model.

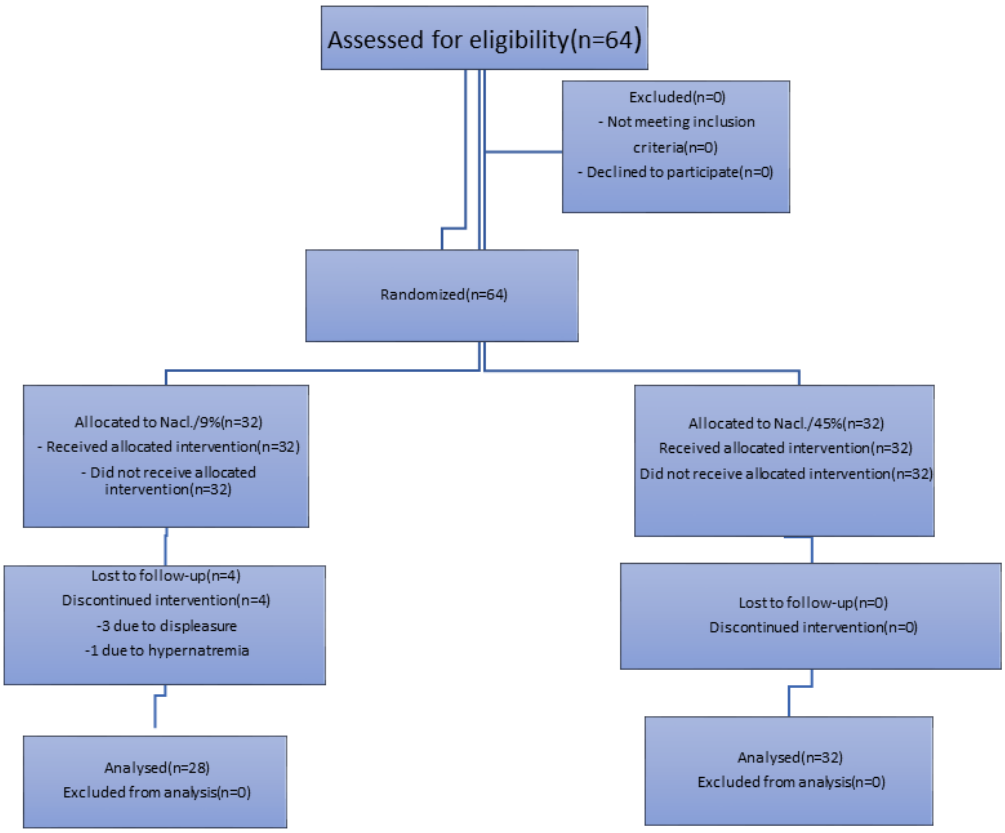

Figure 1. Schematic flow diagram of randomized controlled trial to compare effect of maintenance intravenous fluid therapy on plasma sodium

Table 1. Comparison of the demographic and biochemical characteristics of participants before intervention

Variables	Therapeutic group		*P*	Confidence interval 95%
	Saline 0.9%	Saline 0.45%		
Age†	30.77	30.27	0.91	–
Sex:†† - male	19(67.9%)	20(62.5%)	0.66	
-female	9(32.1%)	12(37.5%)		
Sodium§	139.03± 4.15	138.96± 3.65	0.94	1.94 - 2.08
Urinary Output§	1538.67± 5	1853.43	0.21	-818.871-189
Systolic Pressure†	31.64	29.50	0.21	–
Heart Rate†	27.59	33.05	0.226	–
Potassium†	29.89	31.03	0.801	–
Sugar†	27.82	32.84	0.266	–
BloodUrea Nitrogen†	29.23	31.61	0.599	–
Creatinine†	24.93	35.38	0.021	–
PH†	29.71	31.19	0.744	–
Bicarbonate†	31.61	29.53	0.646	–
Diastolic Pressure†	30.93	30.30	0.855	–
Urine Specific Gravity†	30.73	30.30	0.923	–

† Mann-Whitney test was used and mean rank has reported
†† Chi-square test was used
§ Independent Samples T Test was used and mean± standard deviation has reported

Table 2. Comparison of the mean/ mean rank of biochemical factors in two therapeutic groups after intervention

Variables	After Intervention		*P*
	0.9% saline	0.45% saline	
Sodium†	139.39 ± 0.9	137.49 ± 0.64	0.94
Potassium†	4.02 ± 0.09	4.02 ± 0.08	0.21
Creatinine†	1.01 ± 0.06	0.99 ± 0.06	0.21
Systolic Blood Pressure††	31.07	30	0.81
Heart Rate†	76.85 ± 13.42	79.90 ± 12.94	0.37
Sugar††	30.77	30.28	0.91
Blood Urea Nitrogen†	20.90 ± 8.02	20.92 ± 7.94	0.99
PH†	7.41 ± 0.069	7.43 ± 0.052	0.27
Bicarbonate††	29.91	31.02	0.8
Diastolic Blood Pressure††	31.32	29.78	0.73

Independent Samples *t-t*est was used, and mean± standard deviation has reported †
†† Mann-Whitney test was used, and the mean rank has reported

Discussion

Hyponatremia is caused by the reduction of sodium uptake, increase in water uptake, or disruption in free water clearance from kidneys. This disorder may progress following disorder in water clearance when the patient is receiving hypotonic fluids. Arginine vasopressin leads to an increase in permeability of collector channels to the water content of kidneys and water retention in the body. Hospitalized children often have more than one driver for the secretion of arginine vasopressin (including postoperative status, losing blood, vomiting, and pain). These factors usually are along with disorder in free water clearance. Therefore, hypotonic fluids, having more free water ration compared to isotonic fluids, lead to a positive balance of free water in these patients (9).

The results of the current study indicated that the mean level of plasma's sodium in patients admitted in ICU has no statistically significant difference before and after intervention in two groups of 0.9% saline and 0.45%

saline. The obtained results were aligned with the results of a study by Maria Clara and colleagues on 50 children undergoing appendectomy surgery. Their results showed that not any change in serum sodium content was made after 48 hours (10).

In another double-blinded study by Jeremy N and his colleagues, 110 admitted children with a mean age of 18 years and one month and normal serum sodium content, requiring more than 48 hours of intravenous fluid therapy, were included. They observed no any considerable change in serum sodium content after 48 hours, [11], which confirms our results.

But the vast majority of studies have reported the high incidence of hyponatremia after receiving hypotonic fluids, which is not consistent with the results of our study (6,9,11-12,14-19). This inconsistency may be due to the fact that most performed studies were focused on children who have a considerable difference in fluid and electrolyte balance with adults. Several characteristics in children account for this difference: 1) larger body surface per mass unit leads to higher subtle water clearance through the skin in children, 2) in children, water forms a higher percentage of body mass, 3) higher metabolisms necessitate more water reception for repulsion of waste materials, 4) in young children, immaturity of some renal clearance regions cause some disorders in fluids and electrolytes clearance, 5) possibility of the presence of some underlying diseases and their effect on fluid and electrolytes balance, in the form of changes in hydration amount and electrolyte content (15).

In addition, most studies have been carried out on surgical patients who have numerous hemodynamic (clinical volume decline, hemorrhage, hypotension …) and non-hemodynamic (pain, nausea, and vomiting, fever, drug abuse…) drivers for the secretion of arginine vasopressin (16).

In one meta-analysis, it was asserted that the segregation of surgical patients from non-surgical patients has been not possible for them. Therefore, based on calculations and descriptions of titles, at least 598 titles from 863 titles included surgical patients. In that case, it was not possible to generalize the results of analyses to all hospitalized children. They have mentioned that the limitation of their study has been the absence of those studies that show 0.45% saline in non-surgical patients in comparison with isotonic fluids (17).

Although in this study, reduction in mean serum sodium, after and before the intervention, did not become significant, 1.47 meq/l reduction in the hypotonic group may clinically face the patients admitted in ICU who have had low initial sodium or are confronting with the danger of an increase in arginine vasopressin, with the risk of hyponatremia. Hence, the administration of isotonic fluids would be more appropriate in preventing hyponatremia in this group. As the 0.36 meq/l increase in isotonic 0.9% saline group in the current study indicates, this fluid is more appropriate in preventing hyponatremia in hospitalized patients compared to the hypotonic intravenous fluid.

Most of the randomized studies and clinical trials also indicate the superiority of isotonic fluids in preventing hyponatremia (18-20).

Moreover, in a study by Horn and colleagues, the authors suggested that using intravenous isotonic fluid is more appropriate than the intravenous hypotonic fluid in relation to sodium level (18).

In this study, we attempted to minimize the role of driving factors of arginine vasopressin secretion and exclude those patients with hypotension, cerebral disorders (trauma, hemorrhage, infection, *etc.*), edema, and volume increase, such as chronic heart, liver, and renal failures, from the study.

The absence of difference in mean serum sodium contents in these two groups shows that selecting isotonic fluids in patients, not in the state of increase of arginine vasopressin or not clinically in the states of volume increase or reduction has no any superiority to hypotonic fluids.

The results of this study indicated that the mean levels of plasma's potassium, bicarbonate, systolic and diastolic pressures, BUN, PH, and BS, before and after the intervention, have no statistically significant difference in two groups, which were consistent with the results of Ahmar Shamim, concerning the stability of these parameters after administration of hypotonic fluid (21). The change in urinary output also was not significant in that study, which is consistent with our study.

Based on the results of this study, it was shown that the administration of maintenance hypotonic fluids has been appropriate for the patients who had normal serum sodium content and were not in clinical conditions of ADH increase and will not face them with the risk of hyponatremia.

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