Study of Hypotonic Versus Isotonic Fluids as Maintenance Fluid in Children with Acute Conditions

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Abstract

Background: It is a common practice to give intravenous fluids (IVF) that contain lower sodium concentration than is found in human serum (hypotonic saline) as maintenance fluids

Aim: To study the incidence of hyponatremia in children receiving hypotonic versus isotonic fluid as maintenance fluids.

Methods: This was a prospective randomized controlled trail, participants being 180 children with acute conditions requiring a minimum 50% of total maintenance fluid by intravenous route at-least for 24 hour period. Patients were randomized into three groups of 60 each, receiving intravenous maintenance fluids, 0.22DNS (hypotonic), 0.45DNS (hypotonic) and 0.9DNS (isotonic). Blood samples were collected on admission for baseline serum sodium and repeated after 24 hours.

Results: Patients receiving hypotonic fluids (0.22 and 0.45 DNS) showed decrease in mean sodium levels at 24 hours which was statistically significant ($p<0.05$) and patients receiving isotonic fluids (0.9DNS) showed increase in mean sodium levels without causing hypernatremia and was statistically significant ($p<0.05$).

Conclusion: Patients receiving isotonic fluids had shorter duration of hospital stay.

Key words: Hyponatremia, hypotonic fluids, isotonic fluids.

Introduction

Meningitis, encephalitis, brain tumors, septicemia, pneumonia, asthma, bronchiolitis, head injury and post- operative conditions are common causes of hospital admission in children. It is common practice to give intravenous fluids (IVF) as maintenance fluids in the above conditions either due to poor tolerance of enteral fluids, poor conscious state or risk of pulmonary aspiration and to maintain electrolyte balance[1].

There is no agreement as to what the sodium concentration of these maintenance fluids should be. Traditionally, the common practice is to give IVF that contains lower sodium concentration than is found in human serum (hypotonic saline). The basic principal for prescribing maintenance IVF in children were laid in 1940s and 1950s which culminated with Holliday and Segar's landmark paper in 1957[2]. Holliday and Segar's traditional guidelines calculate maintenance fluid volumes to match Electrolyte free water (EFW) from estimates of water evaporation (heat dissipation) and caloric expenditure (heat production). These calculations result in the convenient estimate for EFW requirements for maintenance therapy of 100 ml/100kcal/day. The primary basis for current recommendation of prescribing 3.0 and 2.0 mEq/100kcal/24hr for sodium and potassium, respectively, in maintenance fluids is that it roughly reflects the electrolyte composition of breast milk and cow milk. However the optimal composition and volume of IVF in acute conditions to maintain hydration and electrolyte balance, remains uncertain.

Patients with acute conditions have low sodium levels and adverse effects like hyponatremia sometimes occur with large amounts of hypotonic saline. It has been proposed to use IVF that have sodium concentration similar to that of a healthy person (isotonic saline). Sick children who present with

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central nervous system disturbances (meningitis, brain tumors, head injury), pulmonary diseases (pneumonia, asthma), malignancies, postoperative states are much more likely to have nonosmotic stimulus for antidiuretic hormone (ADH) production further exacerbating hyponatremia. The estimation of EFW requirement has been challenged for several reasons like these studies are based on healthy and not in diseased states and there is impaired ability to excrete EFW due to ADH secretion during acute illness. Hyponatremia is the commonest electrolyte disorder amongst hospitalized children and the association between hypotonic maintenance solution and risk of hyponatremia has now been repeatedly identified in several studies [3]. The incidence of hospital acquired hyponatremia has been reported to be as high as 50% in some instances. Hoorn et al. demonstrated that the most important factor contributing to hospital acquired hyponatremia in their case control study was hypotonic fluid administration[4]. The contributing factors to hyponatremia in sick children comprise a combination of nonosmotic stimuli for ADH release such as subclinical volume depletion, pain, nausea, stress, edema forming conditions. The symptoms of hyponatremia may be nonspecific and subtle such as nausea and vomiting[4] which typically attributed to other causes until more overt symptoms of cerebral edema develop. The morbidity related to hospital acquired hyponatremia in children receiving hypotonic maintenance solution is increasingly recognized[5,6]. Children are at greater risk of neurological sequel because their brains have a larger intracellular fluid per total skull volume [7].

The reluctance to use isotonic solutions as maintenance fluids in children is primarily attributed to the risk of developing hypernatremia. Excessive renal solute loading, agreater than recommended daily nutritional sodium supply and urinary tonicity that is less than or approximates half normal saline are the commonest arguments against the use of isotonic fluids in children[8]. However a systematic review of studies conducted by six different groups Burrows (1983), Brazel (1996), Dagli (1997), Neville (2006), Hoorn (2004) and Wilkinson (1992) showed none of the participants had hypernatremia[3]. Powell et al. observed that the administration of isotonic maintenance solution in sick children with elevated ADH resulted in more rapid return of ADH to normal concentrations, when compared to hypotonic fluids[9]. Naville et al. demonstrated in a prospective randomized study of IVF solutions in children with gastroenteritis that isotonic fluid protected against the development of hyponatremia without causing hypernatremia, when compared to hypotonic fluids[10].

The present study aims to address the issue of ideal maintenance fluid through a randomized control study. Hnce the objective was to study hypotonic versus isotonic fluids as maintenance fluid in acute conditions in children and to study the incidence of hyponatremia in children receiving hypotonic versus isotonic fluid as maintenance fluids.

Materials and Methods

Prospective Randomized control Trail –single blinded, participants being 180 children with acute conditions requiring a minimum 50% of total maintenance fluid by intravenous route at-least for 24 hour period in between the age group of 6months to 12years at Teaching Hospital Bidar with enrollment period of 12 months from May 2016 to April 2017.

Inclusion criteria: conditions having nonosmotic stimulus for antidiuretic hormone like central nervous system disturbances (meningitis, brain tumors, head injury), pulmonary diseases (pneumonia, asthma), malignancies, postoperative states.

Exclusion criteria: conditions having osmotic stimulus for antidiuretic hormone likenephrosis, cirrhosis, hypovolemia, congestive cardiac failure, hypoalbuminaemia.

An informed and written Consent was taken from the parents. Patients were prospectively randomized to one of the three groups in 1:1:1 proportion and either received 0.22% DNS (hypotonic), 0.45%DNS (hypotonic) or 0.9 DNS (isotonic). Blood samples were collected on admission for baseline serum sodium, potassium, urea, creatinine, blood sugar level and urine specific gravity and repeated every 24hrs till minimum 50% of total maintenance fluid was administered by intravenous route. Recordings less than 135 meq/L were taken as hyponatremia and more than 145meq/L as hypernatremia. To compare pre and post values paired t test was used and to compare the mean values between different groups unpaired t test was used.

Results

Of the 180 patient included, no patient discontinued the study. Table1 shows there was no significant difference in the age amongst those allocated to hypotonic and isotonic group with mean age of 4.5yrs, 5.2yrs and 4.6yrs in 0.22DNS, 0.45DNS and 0.9DNS respectively. Of the total 180 patients, 19 (10.55%) had

hyponatremia on admission with 14 patients in hypotonic group and 5 patients in isotonic group. The mean sodium level (mEq/L) on admission was 138.40 (SD 3.52) in 0.22DNS, 138.60 (SD 3.09) in 0.45DNS and 138.46 (SD 3.0) in 0.9DNS. The difference in mean was not statistically significant (p>0.05).

Table 1. Profile of cases on admission

	0.22%DNS	0.45%DNS	0.9%DNS
Age	Mean- 4.5years Lowest age- 0.5years Highest age- 12years	Mean- 5.2years Lowest age- 0.5years Highest age- 12years	Mean- 4.6years Lowest age- 0.5years Highest age- 12years
Total number of cases	60	60	60
Hyponatremia on admission	09	05	05
Serum sodium (mEq/L) on admission	Mean- 138.40 Lowest- 131 Highest- 144	Mean- 138.60 Lowest- 128 Highest- 144	Mean- 138.46 Lowest- 130 Highest- 143.80

Table 2. Serum sodium levels when hypotonic fluids were used (combined)

	Mean Sodium Level (mEq/L)					
0.22 DNS N=(60)	0 hour		24 hours		Paired t test t value	P value
	Mean	SD	Mean	SD		
	138.40	3.52	136.56	3.12	8.388	<0.05
0.45DNS N=(60)	Mean Sodium Level (mEq/L)					
	0 hour		24 hours		Paired t test t value	P value
	Mean	SD	Mean	SD		
	138.60	3.09	136.80	2.79	9.27	<0.05
HYPOTONIC FLUID n=(120)	Mean Sodium Level (mEq/L)					
	0 hour		24 hours		Paired t test t value	P value
	Mean	SD	Mean	SD		
	138.58	3.315	136.79	2.945	11.76	<0.05

Table 3. Serum sodium levels when isotonic fluids (0.9 DNS) were used

	Mean Sodium Level (mEq/L)					
0.9 DNS N=(60)	0 hour		24 hours		Paired t test t value	P value
	Mean	SD	Mean	SD		
	138.46	3.00	139.49	2.60	5.05	<0.05

Table 4. Changes in serum sodium levels after 24 hours of admission

Total mean sodium level (mEq/L) n= 180					
0 hour		24 hours		Paired t test t value	P value
Mean	SD	Mean	SD	5.411	< 0.05
138.53	3.207	136.68	3.122		

Table 5. Comparison of sodium levels (mEq/L) between hypotonic and isotonic fluid groups

Group	0.22DNS	0.45DNS	Group	0.45DNS	0.9DNS
Mean	136.7228	136.8237	Mean	136.8237	139.4907
SD	3.1201	2.7948	SD	2.7948	2.6018
SEM	0.4028	0.3608	SEM	0.3608	0.3359
N	60	60	N	60	60
Unpaired t test value= 0.1865		**p value >0.05**	**Unpaired t test value=5.410**		**p value <0.05***
Group	**0.22DNS**	**0.9DNS**	**Group**	**Hypotonic**	**Isotonic**
Mean	136.7228	139.4907	Mean	137.6791	139.4907
SD	3.1201	2.6018	SD	3.1091	2.6018
SEM	0.4028	0.3359	SEM	0.2317	0.3359
N	60	60	N	120	60
Unpaired t test value= 5.2773		**P value<0.05***	**Unpaired t test value= 4.063**		**p value<0.05***

Table 2 shows when analysis of hypotonic group together (0.22%DNS+0.45DNS) (n=120) was done, the mean sodium level (mEq/L) on admission was 138.58 (SD 3.315). This mean sodium level decreased to a mean sodium level of 136.79 (SD 2.945) at 24 hours. The drop in mean sodium level after infusion of hypotonic fluid group reached stastistical significance (p<0.05).

Table 2 shows when the subgroups in hypotonic fluid group were analyzed separately the mean sodium level in 0.22DNS group was 138.40 (SD 3.52) and in 0.45DNS group was 138.60 (SD 3.09) on admission. This mean sodium level decreased to a mean sodium level of 136.56 (SD 3.12) and 136.80 (SD 2.79) in 0.22DNS group and 0.45DNS group respectively at 24 hours. The drop in mean sodium level after 24hrs infusion of 0.22DNS and 0.45DNS reached stastistical significance (p<0.05).

Table 3 shows in isotonic group (0.9DNS) (n=60), the mean sodium level on admission was 138.46 (SD 3.0). This mean sodium level increased to 139.49 (SD 2.60) at 24 hours. The increase in mean sodium level after 24hr infusion of isotonic fluid reached statistical significance (p<0.05).

Table 4 shows (n=180) mean sodium level combining 0.22DNS, 0.45DNS and 0.9DNS groups on admission was 138.53 (SD 3.20). This mean sodium level decreased to a mean sodium level of 137.87 (SD 3.02) at 24 hours. The drop in mean sodium level after infusion of combined hypotonic fluid and isotonic fluid reached statistical significance (p<0.05).

Table 5 shows the following –

- When compared the difference between 0.22DNS and 0.45DNS groups, there was no significant difference in mean sodium levels and did not reach statistical significance (p>0.05).
- When compared the difference between 0.22DNS and 0.9DNS groups, there was significant difference in mean sodium levels and reached statistical significance (p<0.05).
- When compared the difference between 0.45DNS and 0.9DNS groups, there was significant difference in mean sodium levels and reached statistical significance (p<0.05).
- When compared the difference between different groups i,e hypotonic group (0.22DNS and 0.45DNS) and isotonic group (0.9DNS), there was significant difference in mean sodium levels and reached statistical significance (p<0.05).

Discussion

Out of 180 patients, none had hypernatremia on admission. After infusion of 0.22DNS and 0.45DNS (hypotonic group) for 24 hours, none of the patients developed hypernatremia and after infusion of 0.9DNS (isotonic group) for 24hours, one patient developed mild hypernatremia. A randomized controlled open study was done by P. Alvarez Montanana (2008),[11] similar results were observed. One patient developed hypernatremia after 24 hours infusion of 0.9DNS. The increase in percentage hypernatremia did not reach statistical significance in both the studies (p>0.05), Brazel (1996)[12], Dagli (1997)[13], Neville (2006)[10], Hoorn (2004)[4] and Wilkinson (1992)[13] showed none of the participants had hypernatremia. This supports the hypothesis that infusion of isotonic fluids in sick children does not cause significant hypernatremia.

The probable reason for a drop in sodium levels from the baseline compared to after 24 hours of hypotonic fluid is the inability to excrete the electrolyte free water due to ADH secretion, as ADH

limits renal water excretion in this settings, even in the presence of a low plasma osmolality. As a result, hyponatremia occurs due to a positive balance of EFW in association with impaired ability to excrete hypotonic urine. A randomized controlled open study was done by P. Alvarez Montanana (2008). "The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics"[11]. One hundred twenty two children hospitalized in intensive care unit requiring maintenance fluid therapy were randomized to receive isotonic fluids (Sodium concentration of 140 mEq/L) or hypotonic fluids (Sodium concentration in between 20 and 100 mEq/L). The mean sodium level on admission was 137mEq/L.This mean sodium level decreased (n=23) to 136.2 mEq/L after infusion of hypotonic fluid for 24 hours and the mean sodium increased (n=23) to 138.9 mEq/L after 24 hours of isotonic fluid infusion. Similar results were observed in our study.However it did not reach statistical significance unlike our study. But this clearly demonstrates that infusion of hypotonic fluids exacerbates hyponatremia in sick children.

Hypotonic maintenance fluids exacerbate the fall in plasma sodium as it provides an exogenous source of EFW during acute illness when ADH secretion limits the renal water excretion of EFW. A recently conducted systematic review of maintenance fluids for hospitalized children revealed that the use of hypotonic fluids remarkably increased the odds of developing hyponatremia by 17 times when compared to isotonic fluids[3]. Unacceptably high adverse neurological outcome rates of up to 30% are still reported. The risk of hyponatremia and adverse neurological outcome in these patients is seldom recognized or anticipated[14] and is thus compounded by the administration of hypotonic solutions, and minimal electrolyte monitoring. Children are at higher risk of adverse neurological outcome because their brains have a larger intracellular fluid volume per total skull volume[7].

Therefore use of isotonic saline may reduce the morbidity and mortality in hospitalized sick children requiring maintenance intravenous fluids. This is especially true in many hospitals in resource poor countries, where it is not possible to measure serum electrolyte routinely, so strategies for fluid management needs to be relooked and protocolized.

Conclusion

The mean sodium levels were lower at 24 hours compared to baseline sodium levels in sick children receiving hypotonic fluids and the drop in mean sodium levels was statistically significant.

The original guidelines for maintenance fluid by Holliday and Segar may not be applicable in the era when the complexity and the severity of illness seen in hospitalized children who receive intravenous fluid therapy has radically changed and inappropriate ADH secretion is more likely. We believe that hospital acquired hyponatremia unnecessarily puts children at risk for the development of adverse neurologic complication and can be prevented by use of isotonic fluids.

There was increase in mean sodium levels in sick children receiving isotonic fluids and the increase in mean sodium levels was statistically significant. However there was no significant increase in number of cases of hypernatremia after infusion of isotonic fluids.(serum sodium levels did not cross the upper limit of normality i,e 145mEq/L).

No deaths were reported in hypotonic and isotonic groups.

We conclude that although in healthy subjects the ratio of water to sodium in serum is tightly controlled by ADH-kidney axis, hyponatremia is common presentation in sick children due to ADH excess. Routine administration of hypotonic parenteral fluid to these sick children can result in exacerbation of hyponatremia with resulting prolonged hospital stay, morbidity and even mortality too. We suggest hypotonic fluids should not be used routinely in sick children. Isotonic fluids improve the mean sodium levels in sick children without causing significant hypernatremia. With respect to safety, there are only theoretical concerns that hypernatremia and fluid overload are risks of using isotonic saline as routine maintenance and the same was not corroborated by our study. Isotonic fluids can be considered as prophylaxis against hyponatremia, except in the setting of free water deficit or ongoing free water losses.

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Conflict of interest: Nil
Source of funding: Nil

Date received: July 19th 2017
Date accepted: September 2nd 2017