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To study the Mean serum sodium level and adverse events associated with infusion of isotonic saline (0.9%NS) compared with hypotonic saline (0.45%NS) as maintenance fluids in children

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Background: The purpose of intravenous (IV) fluid therapy is replacement of water and mineral of the body fluids in patients who could not maintain hydration orally.[1]

For almost half a century, pediatricians have ordered "maintenance" intravenous (IV) fluids for children according to the guidelines set out by Holliday and Segar:.[2] Based on these recommendations for water intake, and on the estimated daily sodium and potassium needs of 3 milli equivalents and 2 milliequivalents per 100 kcal per day respectively, a hypotonic solution (0.2% saline) was recommended.[3,4] The wisdom of this approach to IV maintenance fluid therapy has been questioned recently.[5-8] Several authors have argued that administration of hypotonic fluids to hospitalized children [13].Although the best choice of solution for IV maintenance needs has not yet been defined, many clinicians commonly prescribe 0.45% saline as a sort of 'compromise' between the traditional 0.18% saline and a complete switch to isotonic fluids. Therefore, we chose to compare 0.9% saline in 5.0% dextrose to 0.45% saline in 5.0% dextrose.

Material and Methods: Prospective and Interventional Randomized single blinded Comparative study (computerized block randomization). Was carried out in Department of pediatrics Hindu Rao Hospital from 2108 to 2019 The objectives were to compare mean serum sodium levels in both groups after24 hrs., and 48 hrs., of initiation of therapy, compare incidence of hyponatremia and study signs of fluid overload.

Children of age group 1 year to 12 years suffering from Severe Pneumonia, meningitis, encephalitis, Menin go encephalitis, hepatitis and infections admitted in pediatric emergency and ward requiring IV maintenance fluid having normal serum sodium levels were included All eligible patients were randomized to receive either Isotonic (0.9% NS in 5% Dextrose), at the rate of standard maintenance volume or hypotonic (0.45%NS in 5% Dextrose), at rate of standard maintenance volume. Randomization sequence was generated using Technique computerized block randomization. The data was entered

in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results: Significant changes were observed in serum sodium, mean serum sodium in isotonic group was more as compared to hypotonic group at 24 and 48 hrs. of IV fluid administration. No adverse events were seen in either group

Keyword: Isotonic, Hypotonic, Hypo natremia and Hyper natremia.

Introduction

The purpose of intravenous (IV) fluid therapy is replacement of water and mineral of the body fluids in patients who could not maintain hydration orally.[1]For almost half a century, pediatricians have ordered "maintenance" intravenous (IV) fluids for children according to the guidelines set out by Holliday and Segar: 100 ml/ kg/ day for the first 10 kg, plus 50 ml/kg/day for the next 10 kg, plus 20 ml/kg/day for each remaining kilogram.[2] Based on these recommendations for water intake, and on the estimated daily sodium and potassium needs of 3 milliequivalents and 2 milliequivalents per 100 kcal per day respectively, a hypotonic solution (0.2% saline) was recommended.[3]

administration of hypotonic fluids to hospitalized children - many of whom have a non-osmotic stimulus for anti-diuretic hormone (ADH) secretion - may lead to clinically important hyponatremia[4].

Iatrogenic hyponatremia has been the reported cause of neurological injury or death in more than 50 cases[5].Concerns regarding hyponatremia have led some authors to recommend using isotonic saline as the routine maintenance solution for hospitalized patients, reserving hypotonic fluids for exceptional situations. Isotonic saline administration may result in an increase in serum [Na] and/or chloride, but has not been shown to increase the risk for hypernnatremia. Six randomized trials have demonstrated significantly greater drops in [Na] among patient receiving hypotonic solutions compared with those receiving isotonic solutions [6]. Although the best choice of solution for IV maintenance needs has not yet been defined, many clinicians commonly prescribe 0.45% saline as a sort of 'compromise' between the traditional 0.18% saline and a complete switch to isotonic fluids. Therefore, we chose to compare 0.9% saline in 5.0% dextrose to 0.45% saline in 5.0% dextrose respectively.

Material and Methods

Prospective and Interventional Randomized single blinded Comparative study was carried out in Department of pediatric and pediatric emergency Hindu Rao hospital (a tertiary care hospital in north Delhi from Nov 2018 to May2019 in 1 to 12 years Age group. Main Objectives were To compare mean serum sodium levels in both groups after 24 hrs. and 48 hrs., of initiation of therapy and to study incidence of hyponatremia (serum sodium <135mEq/L) and hypernatremia (serum sodium >145 mEq/L).After obtaining clearance from institutional ethical committee Children of age group 1 years to 12 years admitted in Pediatric emergency and ward requiring IV maintenance fluid having normal serum sodium levels, and suffering from Severe Pneumonia, meningitis, encephalitis, Meningoencephalitis, hepatitis and infections were included Children with hemodynamic instability, and suffering from Acute or chronic Kidney Disease, Acute gastroenteritis, and cardiac dysfunction were excluded.

65 Patients each in Isotonic and hypotonic group were included sample size was derived from Statistical formula. All eligible patients were randomized to receive either Isotonic or Hypotonic at the rate of standard maintenance volume. Randomization sequence was

generated using Technique computerized block randomization.

Maintenance fluid volume for administration was calculated using Holliday and Segar formula. Both groups received 1 ML of potassium chloride per 100 ML of intravenous fluids.

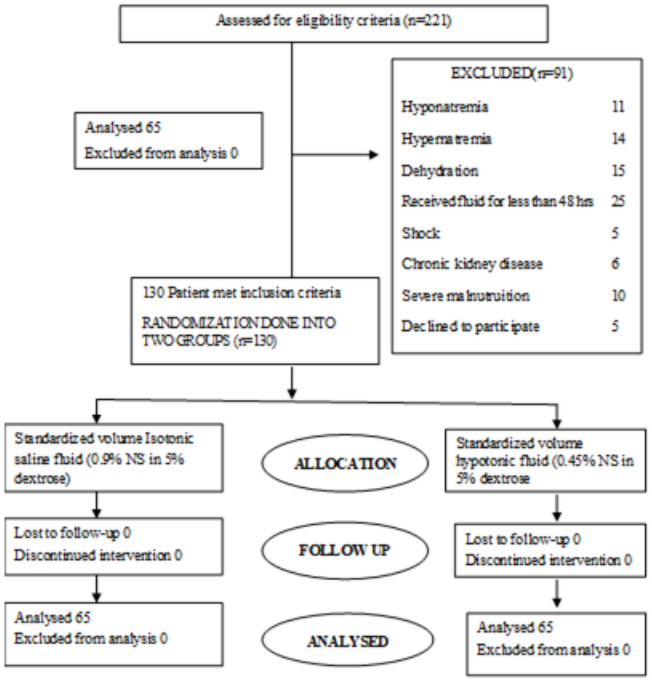
Baseline demographic and laboratory characteristics were noted at enrolment. All patients were monitored clinically for symptoms and signs of dysnatraemias and signs of fluid overload or dehydration throughout the study period. Clinical assessment, including Weight and Blood pressure were done every 24 hours. Measurement of Weight in Kg by digital weighing scale at an interval of 0 hrs., 24 hrs. and 48 hrs.

Approximately 2 ml of Venous blood sample was withdrawn at 0 hrs., 24hrs.and 48 hrs. of starting of IV fluid for measurement of serum sodium, potassium, blood urea, creatinine.

During Intravenous fluid therapy, children were observed for clinical features of Dyselectrolytemia (Seizures, letharginess, irritability, coma) and fluid overload (weight gain>10 % from the base line) and outcome, duration of hospitalization were observed at the time of discharge.

In case of any clinical features of hypo natremia / hyper natremia or fluid overload, plan was to manage according to standard protocol and exclusion from the study. Categorical variables were presented in number and percentage (%) and continuous variables was presented as mean ± SD and median Data was entered in MS EXCEL Spreadsheet and analysis was done using SPSS Version 21.0.

Fig 1: Algorithm of Methodology



Results

Sodium levels were higher at 0 hours in hypotonic group (137.29±2.582 mg/dl) as compared to is otoni group (136.24±1.479mg/dl), but this association was not significant (P>0.05). Sodium levels were high at 24 hours in isotonic group (138.47±2.250 mg/dl) as compare to hypotonic group (136.20±2.867mg/dl), but this association was not significant (P>0.05).but serum Sodium levels were high at 48 hours in isotonic group (140.35±2.400 mg/dl) compare to hypotonic group (135.21±2.355 mg/dl).This association was statistically significant. (P < 0.05) There was no statistically significant change in Potassium level. (Fig 2)

Table 1: Mean sodium at 0hrs,24 hrs. and 48 hrs. t test distribution (mean + SD) and ANOVA test.

N=65		0hrs (mEq/L)	24hrs (mEq/L)	48hrs (mEq/L)	Anova p value
Serum Sodium	Isotonic (0.9%NS in 5% Dextrose)	136.24±1.479	138.47±2.250	140.35±2.400	<0.05
	Hypotonic (0.45% NS in 5%	137.29±2.582	136.20±2.867	135.21±2.355	

	Dextrose)				
Serum Potassium	Isotonic (0.9%NS in 5% Dextrose)	3.61±0.141	3.80±0.215	3.99±0.222	>0.05
	Hypotonic (0.45% NS in 5% Dextrose)	3.60±0.179	3.88±0.244	3.95±0.344	

After 24 hours of receiving fluid it was observed that 12 children were of mild hyponatremia (130-135 mEq/l) in hypotonic group and In isotonic group this number was 3 which was not statistically significant (p>.o5)(Fig 3) ,after 48 hrs. of intravenous fluid therapy mild hyponatremia increased to 27 in hypotonic group which was statistically significant (p<.05) as compared to only two cases of mild hyponatremia that occurred in isotonic group there was no case of mild hypernatremia(serum sodium more than 145 mEq/l) obtained in either group at 48 hrs. .(Fig 4)

No symptomatic hyponatremia and hypernatremia case was seen in any group.

Table 2**:** Distribution between serum sodium (24hrs) in isotonic and hypotonic group.

Serum Sodium (24hrs)	**Type of Fluid**				**Total**	
	Hypotonic (0.45%NS)		**Isotonic (0.9%NS)**			
	Freq	%	Freq	%	Freq	%
Mild Hyponatremia (130-135meq/L)	12	18.4	3	4.6	28	21.5
Mild Hypernatremia (145-150 mEq/L)	0	0.0	2	3.0	2	1.5
Normal (135-145 mEq/L)	53	81.5	60	92.3	100	77
Total	65	100.0	65	100.0	130	100.0

Table 3**:** Distribution between serum sodium (48hrs) in isotonic and hypotonic group.

Serum Sodium (48hrs)	**Type of Fluid**				**Total**	
	Hypotonic (0.45%NS)		Isotonic (0.9%NS)			
	Freq	%	Freq	%	Freq	%
Mild Hyponatrimia (130-135mEq/L)	27	41.5%	2	3.1	45	34.61
Normal (135-145 mEq/L)	38	58.5%	63	96.9	85	65.3
Total	65	100.0	65	100.0	130	100.0

More number of hyponatremia cases observed in isotonic and hypotonic group at 48 hrs of study, in hypotonic group hyponatremia case were 27 constituting 41.5% of total cases where as in isotonic cases 2 cases of hyponatremia were seen 3.1%. This association was statistically significant. (Fig 4).

Discussion

This is one among the few studies done prospectively to assess the impact of prescribing isotonic intravenous maintenance fluids on serum sodium changes and other associated complications in the age group between 1 and 12 years.

In a population of general pediatric patients outside the PICU, there was no significant difference in mean serum sodium levels at 24 and 48 hours between those administered isotonic or hypotonic IV maintenance fluids. But results of our study showed that the mean variance of serum sodium over 0, 24 and 48 h is statistically

significant. Mean serum sodium levels were high in isotonic group at 24 hours (138.47±2.250 mEq/L) and 48 hours (140.35±2.400 mEq/L) compare to hypotonic group (136.20±2.867 mEq/L and135.21±2.355 mEq/L). This association was statistically significant. There were no associated adverse events or hypernatremia observed. In a study by Friedman JN et al .[7], they observed that patients receiving isotonic maintenance fluids had a small increase in serum sodium levels at 24 and 48hours, these increases were not clinically significant Similar study conducted by Saba TG et al. [8] on a sample size of 16 children had increase in serum sodium in both isotonic 0.9% NS group (+.20 mmol/L/h) and hypotonic 0.45% (+0.08). Shamim A et al[9]. in their RCT observed significant changes in sodium level mean serum sodium in Isotonic group was constant over initial 24 hours thereafter, an increase in serum sodium was observed between 24 hours and 48 hours (4.3mEq/L,95% CI :0.1,8.4 mEq/L). In Hypotonic group there was significant decline in mean serum sodium level at 24 hrs., and the decline persisted till end of study (4.9 mEq/l).

In present study at 0 hours 130 patients were included having serum sodium in normal range.

At 24 hours mild hyponatremia cases were increased to12 in hypotonic group and in isotonic group there were 3 cases of mild hyponatremia and 2 cases of mild hypernatremia cases in isotonic group but there was no hypernatremia cases in hypotonic group. This association was not statistically significant. (P>0.05). At 48 hours out of mild hyponatremia cases 93.1% belongs to hypotonic solution group and only 6.9% patients belong to isotonic solution group. Normal sodium level in patients were more in isotonic group (96.9%) compare to hypotonic solution (58.5%) group. This association was statistically significant. No case of hypernatremia was found in isotonic and hypotonic group. (Fig 5).

Table 4: Comparison table showing cases of hyponatremia in various studies.

Sn.	Authors	Year of study	Sample size	Age group	Cases of hyponatremia in isotonic group	Cases of hyponatremia in Hypotonic group
1	Yung et al.[7] (0.9% & 0.18%)	2005	53	1-12 years	1/25	7/28
2.	Montanana, Alapont, Ocon et al.[10]	2006	122	1 month – 18 years	3/63	0/59
3.	Kannan Lodha Vivekanandhan et al.[11](0.9% &0.18%)	2006-08	167	3 month-12 years	7/1000 patient days	53.6 cases/ 1000
4.	Rey, Acros Henandez et al.[12](0.33% and 0.9%)	2009	125	1 month-60 months	03/62	15/62
5.	Shamim Afzal et al.[9](0.18% NS & 0.9% NS)	2009	60	6 months to 12 years	4/30	13/30
6.	Raksha, Dakshayani Premlatha[13] (0.9% & 0.18%)	2011	240	1 month-18 years	09/120	20/120
7.	Saba, Fairbairn,	2011	59	3 months-	0/55	0/55

	Houghton.[8](0.9% &0.45%)			18 years		
8.	Friedman Degroot Geary et al[7](0.9% & 0.45%)	2012	110	1 month-18 years	1/54	2/54
9.	Fahimi Aghajani, Karahroudi et al.[14](100Meq/l & 50Meq/l)	2012	108	1 to 14 years	7/46	14/53
10.	Almeida Hl, Mascarenhas, Loueiro[15] (0.9% & 0.45%)	2013	233	1 day-18 years	7/103	14/130
11.	Present study	2018-19	130	1 year-12 years	2/65	27/65

In this study no adverse events of fluid overload weight gain oedema complications due to dyselectrolytemia was noted out of 65 child 27 child developed mild hyponatremia in Hypotonic group after 48 hours of receiving Intravenous fluid was asymptomatic and did not require any intervention during observation period .Kannan et al.[11] in their RCT observed 2 adverse events one patient developed hypernatremic encephalopathy this child was having Acute intermittent porphyria .Another Child expired cause of death was ARDS and he had normal serum sodium throughout the study period**.** Similar to Present study Montanana et al.[10] did not observe any adverse effects other then hyponatremia in any other group. Saba TG et al.[8] did not observed any adverse events in their RCT. Shamim A et al.[9] did not observed any adverse events related to dysnatraemias in either intervention group. No mortality occurred during the observation period.

Conclusion

This Study demonstrates that standard volume main tenance isotonic fluid prevents iatrogenic hyponatremia in comparison to hypotonic maintenance fluid in children without inducing a higher incidence of side effects

Recommendation

Use of isotonic saline solution as maintenance fluid therapy is safe and will result in fewer cases of hyponatremia in 1-12 years Age group, without causing adverse effects.

Limitation of study

Sample size of this study was small and hence the results of this study could not be extrapolated to the whole population.

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