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A Randomized Study of Isotonic Versus Hypotonic Maintenance Intravenous Fluids in Hospitalized Children in a Tertiary Institution in Nigeria, Sub-Saharan Africa

Odion-Obomhense Helen K[1]; Ochei Oboratare[2] & Otene Cletus[3]
[1]Paediatric Surgical Unit, Department of Surgery, Delta State University Teaching Hospital, Oghara,
[2]Department of Community Health, Community Medicine, Delta State University Teaching Hospital
[3]Plastic Surgical Unit, Department of Surgery, Delta State University Teaching Hospital, Oghara,
Email: ***drkesoghene@gmail.com ; droboratare@gmail.com; oteneclet@yahoo.com

ABSTRACT: Maintenance intravenous fluids are administered to hospitalized children who cannot maintain adequate hydration through the enteral intake. Isotonic crystalloids have been said to be a safer alternative to hypotonic solutions as intravenous maintenance fluids to prevent hyponatremia; however, in many pediatric units in Nigeria, hypotonic fluids are still routinely administered. This study was done to assess the complications and the change in serum sodium that arose in patients that had either hypotonic or isotonic intravenous fluids pre-operatively and post-operatively for maintenance. The study was a randomized clinical study conducted among children aged 6 months to 17 years, who required intravenous fluids for at least 8 hours. The children used for the study were randomized into three arms; either they received 5.0% dextrose in normal saline or 5% dextrose in ringers' lactate or, 4.3% dextrose in one-fifth saline. The primary outcome variable was to determine acute hyponatremic state; while the secondary outcome variables measured were severe hyponatremia, hypernatremia, or, any adverse events attributable to acute plasma sodium level changes. The study showed a significantly higher risk of acute hyponatremia and severe hyponatremia in patients who received hypotonic intravenous fluids than in patients who received isotonic fluids. However, there was no significant difference found in the risk of hypernatremia in patients who received either hypotonic intravenous fluids or isotonic fluids. Isotonic fluids are safer than hypotonic fluids in hospitalized children requiring maintenance intravenous fluids therapy to prevent hyponatremia.

Keywords: Children; Hyponatremia, Hypotonic Fluid, Isotonic Fluid. Intravenous Fluid

INTRODUCTION

In the pediatric patient requiring surgeries, for good outcomes, attention must be paid to fluid balance for optimal cellular function. Fluids are needed to replace losses from blood, kidneys, and intestines and also losses that cannot be quantified like insensible losses from hypermetabolic conditions like fever[1]. Fluids and electrolytes requirements in pediatrics have been calculated based on Holliday and

Segar recommendations and based on these calculations, fluids, and electrolyte requirements were calculated based on body weight and this produced the hypotonic fluid of 0.18 % dextrose in one-fifth saline (synonymous with 4.3% dextrose in one-fifth saline) that had been adopted worldwide as the ideal fluids for the pediatric patient[2]. This contains 30 milliequivalents of sodium compared to 154 milliequivalents of sodium in 0.9% normal saline, referred to as a crystalloid fluid[3].

In the past, these hypotonic IV maintenance fluids have generally remained the standard of care for pediatric patients.[4-5] However, there is increasing recognition that many hospitalized children secrete an excess of antidiuretic hormone (arginine vasopressin) and in this state when hypotonic fluids are given to children who are prone to have an excess of arginine vasopressin released, the consequence may be pediatric iatrogenic hyponatremia with serious neurological complications. [6-9]. Isotonic crystalloids (with electrolyte composition close to plasma) have been said to be a safer alternative to traditional hypotonic solutions for intravenous (IV) maintenance fluids to prevent this condition[10] and meta-analysis has been done which proved that isotonic fluids are safer than hypotonic fluids in hospitalized patient[11]. However, routinely hypotonic fluids are still been given in many centers in Nigeria. A national survey in Korea revealed that 69.2% of their pediatric residents were still prescribing hypotonic fluids despite mounting evidence of the dangers of hypotonic fluids in the pediatric age group[12] However to the best of our knowledge such a survey is yet to be done in Nigeria. So we decided to conduct this research in our setting first to confirm or refute the side effects of hypotonic fluids. And if adverse effects were seen with hypotonic fluids we hope to educate physicians managing children, particularly in Nigeria on the dangers of hypotonic fluids for maintenance

Objectives

To compare the complication(s) change in serum sodium ([Na]) for patients administered either hypotonic or isotonic IV fluids for maintenance among pediatric surgical patients in a hospital in Nigeria, in Sub-Saharan Africa.

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METHODOLOGY

Study Area

The study was conducted in the emergency room and pediatric surgical ward of Delta State University Teaching Hospital, Oghara (DELSUTH), Delta State, Nigeria.

Study Protocol

The study was to determine the clinical and biochemical outcome in children aged 6 months to 17 years (Table 1) who received isotonic and hypotonic crystalloids solution preoperatively and postoperatively admitted between 1st January 2018 to 1st January 2019. Inclusion criteria were those patients who required surgery and so were placed on nothing by mouth before the intervention. They would also require intravenous fluids for at least 48 hours after surgery when post-operative electrolytes would be taken. Exclusion criteria were for all-day cases, patients with head injuries or orthopedic injuries, or critically ill patients.

Study Design

The study was a randomized clinical study. Written informed consent was obtained from the mother of each child that met the selection criteria; explaining the reasons for the research, the procedure, benefit, and risks. Subsequently, the selected patient was assigned either to the study groups or the control groups by balloting. A ballot paper with either odd or even numbers was offered to parents. The study group received isotonic crystalloids (5.0% dextrose in normal saline or 5% dextrose in ringers' lactate) and the control groups received (4.3% dextrose in one-fifth saline) at a maintenance rate. This maintenance rate was in line with Holliday and Segar's equation of 100mls/kg for the first 10kg, 50mls/kg for the next 10 kg plus the value gotten for the first 10kg which was 1000mls and 20 mls/kg for the next 10 kg plus 1500mls, which was value gotten from first and second kg respectively. This was begun preoperatively however after 24 hours the electrolytes were recorded and then corrected in each group to ensure patients were stable enough for surgery (Table 2). Post operatively the fluids were also given for 24 hours then the serum electrolytes were re-assessed (Table 3). This was when the main outcomes of the research were concluded (Table 4).

Data Collection method: Patients' age, sex, and clinical features were documented in a proforma. The measurement variables were complications of hyponatremia, hypernatremia, and serum sodium. The pre-operative serum sodium was collected and post-operative serum sodium was obtained 24 hours after surgery by venous sampling peripherally and measured by an ion-selective electrode machine. Information on complications was obtained by observation.

Measurement of Variables

Variables were measured as continuous and nominal. Patient were categorised into one of the following group; normal serum sodium if (pNa = 135-145), severe hyponatremia if (pNa <130 mmol/L), hyponatremia if (pNa <135 mmol/L), and hypernatremia if (pNa >145 mmol/L. The primary outcome was acute hyponatremia. Secondary outcomes included severe hyponatremia, hypernatremia, adverse events attributable to acute plasma sodium level changes

Data Analysis

Data were entered and analyzed using SPSS version 16

Ethical Considerations

Ethical approval was obtained from the Research and Ethics Committee, of Delta State University Teaching Hospital. Confidentially was maintained as names were omitted and replaced with codes

Limitations

CT scan could not be done to assess complications like cerebral edema due to cost. Neonates who are younger than 28 days old or in the NICU and neurosurgical patients were excluded.

RESULTS

A total of 62 patients (Table 1) were enrolled and assigned randomly to receive hypotonic intravenous fluids (N = 31) or isotonic intravenous fluids (N = 31). The study showed a significantly higher risk of hypotonic IV fluids for developing hyponatremia and severe hyponatremia than with isotonic fluids at 24 hours post operatively (Tables 3 and 4). It showed that Hypotonic maintenance fluid (4.3% dextrose in one-fifth

saline) significantly increased the risk of hyponatremia, compared with isotonic maintenance fluid (35.5% vs 16.1%; $P=0.022$).

There was a significantly greater fall in serum Na in children who received hypotonic IV fluids versus isotonic IV fluids which was statistically significant (p=0.022). No significant difference was found between the 2 interventions in the risk of hypernatremia (Tables 3 and 4). Of note was that before surgery baseline electrolytes were similar for the 2 groups of the thirty-one children who received the isotonic fluids and hypotonic fluids but as of the second day post operation, of the 31 who received hypotonic fluids; 13 (42%) had hyponatremia, two of these had severe hyponatremia (<130mmol/l), of these two, one had seizures and then the 4.3% dextrose was discontinued, while 18 had normal serum levels of sodium. It was also notable that none had hypernatremia (Tables 2 and 3). For those on isotonic fluids (Tables 3 and4) , 5(16.1%) had hyponatremia on the second-day post-operation, none had severe hyponatremia while 23 (74.2%) had normal sodium levels. Of note was that hypernatremia was observed only in the group who had isotonic fluids given, 3(9.7%).

DISCUSSION

This study revealed that the relative risk of developing mild and moderate hyponatremia (defined as a serum sodium concentration <135 mEq/L and <130 mEq/L, respectively) to be 35.5% (Table 3), in children who were given 4.3 % dextrose in one-fifth saline (hypotonic fluid). These data strongly reveal an increased risk of hyponatremia when children receive hypotonic versus isotonic intravenous fluids. Children who received isotonic fluid had a lower risk of developing hyponatremia (16.1%) as seen in table 3. Though isotonic maintenance fluid increased the risk of hypernatremia it was not statistically significant (4.8% vs 0% $P=0.722$) and none of the children developed clinically relevant hypernatremia or fluid overload. This corroborates with other researchers in 2 large studies published that illustrated that meta-analysis did not find evidence of an increased risk of hypernatremia with isotonic intravenous fluids. These are the study by Friedman et al,[13] there was 1 patient in each randomized group (N = 110) who developed hypernatremia, and in the study by McNab et al,[14] where the incidence of hypernatremia was 4% in the

isotonic IVF group and 6% in the hypotonic IVF group, with no significant difference noted between the 2 groups

Hyponatremia (serum sodium concentration <135 mEq/L) has also been found to be the most common electrolyte abnormality in patients who are hospitalized and on maintenance fluid, affecting approximately 15% to 30% of children and adults [15]. This study also corroborates with the other studies that found that most hyponatremia in patients who are hospitalized is hospital-acquired and related to the administration of hypotonic intravenous fluids in the setting of factors that would elevate antidiuretic hormone concentrations[16]. Hyponatremia occurs due to water being gained and/or a loss of sodium in the extracellular fluid. There are two factors required for it to occur which is the source of water, which are for the surgical children the intravenous fluid therapy administered since they are not taking anything orally, and the presence of the antidiuretic hormone (ADH) which is known to prevent excretion of water[17-18]. Apart from the mechanisms explained above, other studies have shown that hypotonic maintenance fluids increase the incidence of hyponatremia because they can also decrease blood sodium levels in normonatremic patients[19] and so even in elective cases they should be given with caution.

The consequences of hyponatremia are significant, with possibilities of irreversible neurological morbidity and mortality[20]. As seen in this study the incidence of clinical dysnatremia was only seen with hypotonic fluids with a serum sodium level of 130mmol/l which were seizures. In pediatric patients, even a small decrease in sodium concentrations can lead to cerebral herniation, due to the limited room available in the rigid skull to accommodate the swollen brain[21]. Pre-operative hyponatremia was not an independent risk factor for the development of hyponatremia as baseline characteristics were similar for the two groups, with not many differences in serum sodium before intervention and when analyzed was not statistically significant with a p-value being 0.133 (Table 2). For the past 60 years, the prescription for maintenance intravenous fluids for infants and children has been a hypotonic fluid. These recommendations were made on theoretical grounds and were not based on clinical trials[22]. Despite this accepted principle, over the past decade and longer, there have been increasing reports of the deleterious effect of hyponatremia in

the acute care setting with the use of the prevailing hypotonic maintenance solutions with guidelines for the usage of hypotonic fluids [23, 24]. This study showed that isotonic maintenance fluid is significantly safer than hypotonic maintenance fluid in protecting against acute postoperative hyponatremia in children

Table of Randomization

Results

Table 1: Demographics and fluids used

Variables	Frequency (%)
Age	
Infants (0-1 year)	17 (27.4)
Pre-school (1-5 years)	23 (37.1)
School Age (6-12 years)	14 (22.6)
Adolescent (13-17 years)	8 (19.9)
Sex	
Male	40 (64.5)
Female	22 (35.5)
Fluid Use	
4.3% Dextrose in 1/5 Saline	31 (50.0)
5% Dextrose in Saline	
5% Dextrose Ringers	17 (27.4)
	14 (22.6)

Patients Information and type of fluids used*

Plasma sodium level abnormalities were corrected in both groups before the beginning of surgery. Fluids were administered intra-operatively according to the anesthetist's discretion. The criterion for statistical significance was set at $p < 05$

TABLE 2: Type of fluid administered and preoperative serum sodium

	Serum Sodium Level			
	Severe Hyponatremia	Hyponatraemia	Normal Serum Sodium	Total
Fluid Type				
Hypotonic	1 (3.2%)	8 (25.8%)	22 (71%)	31 (100%)
Isotonic	6 (19.4%)	7 (22.6%)	18 (58.1%)	31 (100%)
Total	7 (11.3%)	15 (24.2%)	40 (64.5%)	62 (100%)
Chi value = 4 .033,p-value= 0.133				

Table 3: Results after 24 hours on each type of fluids; hypotonic or isotonic

Fluid	Serum Sodium				Total	P-value
	Severe hyponatremia	Hyponatremia	Normal	Hypernatremia		
Hypotonic	2 (6.5%)	11 (35.5%)	18(58.1%)	0 (0.0%)	31 (100.0%)	
Isotonic	0 (0.0%)	5 (16.1%)	23(74.2%)	3 (9.7%)	31 (100.0%)	
Total	2 (3.2%)	16 (25.8%)	41(66.1%)	3 (4.8%)	62 (100.0%)	0.022

Fluid Administered and Post-Operative Serum Sodium Level
Hypotonic: 4.3% dextrose in one-fifth saline
Isotonic: 5% dextrose saline and 5% dextrose ringers

Table 4: Results after 24 hours on specific fluids

Fluid Type	Serum Sodium				Total	P-value
	Severe hyponatremia	Hyponatremia	Normal	Severe Hypernatremia		
4.3% dextrose in 1/5 saline	2 (6.5%)	11 (35.5%)	18 (58.1%)	0 (0.0%)	31 (100.0%)	
5% dextrose in saline	0 (0.0%)	1 (5.9%)	14 (82.4%)	2 (11.8%)	17 (100.0%)	
5% dextrose ringers	0 (0.0%)	4 (28.6%)	9 (64.3%)	1 (7.1%)	14 (100.0%)	
Total	2 (3.2%)	16 (25.8%)	41(66.1%)	3 (4.8%)	62 (100.0%)	0.044

Type of Fluid Administered and Post-Operative Serum Sodium Level

CONCLUSION

Isotonic maintenance fluids do not increase the incidence of dysnatremias and should be considered the standard maintenance fluids for pediatric patients. However due to concerns about the increased risk of hypernatremia with isotonic saline, (as seen in this study), a physiologically based fluid protocol is suggested to avoid hyponatremia

RECOMMENDATIONS

As a compromise between traditional 4.3persent dextrose in one-fifth saline and complete switching to an isotonic solution, The National Patient Safety Agency, UK recommended 0.45% saline as standard maintenance fluid to avoid the risk of severe hyponatremia[25], however, more research is required here and this product is currently not available in Delta state and perhaps in Nigeria. More research is also required on the appropriate intravenous fluids in neonatal populations due to their undeveloped anatomy and physiology.

LIMITATIONS

This study took place in a pediatric surgical ward; more studies need to be done to assess the outcomes of children admitted to general pediatric wards not requiring surgeries.

CONFLICTS OF INTEREST: The authors had no conflicts of interest.

REFERENCES

1 Hirschl, Ron, et al., editors. "Fluid and Electrolytes." *Pediatric Surgery NaT*, American Pediatric Surgical Association, 2022. *APSA Webapp*, www.pedsurglibrary.com/apsa/view/Pediatric-Surgery-NaT/829017/all/Fluid_and_Electrolytes.

2 Michael MA Tran, Esther M Tantsis, Joanne M Ging. **In children requiring intravenous fluid for hydration maintenance, which out of hypotonic saline and isotonic saline is less likely to result in the development of hyponatraemia? Journal of pediatrics and child health. Volume53, Issue3** March 2017, Pages 309-313

3 Fluids and electrolytes therapy, core concepts of pediatrics, second edition, pages 1 -12, online book; last reviewed March 1st, 2022.

4 Armon K, Riordan A, Playfor S, Millman G, Khader A; Paediatric Research Society. Hyponatraemia and hypokalaemia during intravenous fluid administration. *Arch Dis Child*. 2008; 93(4):285-287.PubMedGoogle ScholarCrossref

5 Freeman MA, Ayus JC, Moritz ML. Maintenance intravenous fluid prescribing practices among paediatric residents. *Acta Paediatr*. 2012; 101(10):e465-e468.PubMedGoogle ScholarCrossref

6 Holliday MA, Friedman AL, Segar WE, et al. Acute hospital-induced hyponatraemia in children: a physiologic approach. J Pediatr. 2004; 145:584–587

.7 Carandang F, Anglemyer A, Longhurst CA, et al. Association between maintenance fluid tonicity and hospital-acquired hyponatremia. *J Pediatr*. 2013; 163(6):1646-1651.PubMedGoogle ScholarCrossref

8 Moritz ML, Ayes JC. Prevention of hospital-acquired hyponatremia: do we have the answers? *Pediatrics*. 2011; 128(5):980-983.PubMedGoogle ScholarCrossref

.9 Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. *Pediatrics*. 2004; 113(5):1279-1284

(Acta Paediatr. 2014 Oct; 103(10):1027-34. doi: 10.1111/apa.12705. Epub 2014 Jul 1.

10 Brazel PW, McPhee IB Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. Spine. 1996; **21**(6):724–727pmid:8882695

11 Wang J, Xu E, Xiao Y. Isotonic versus hypotonic maintenance IV fluids in hospitalized children: a meta-analysis. Pediatrics. 2014 Jan; 133(1):105-13. doi: 10.1542/peds.2013-2041. Epub 2013 Dec 30. PMID: 24379232.

12 Lee JM, Jung Y, Lee SE, et al. Intravenous fluid prescription practices among pediatric residents in Korea. *Korean J Pediatr*. 2013; 56(7):282-285. doi:10.3345/kjp.2013.56.7.282

13 Friedman JN, Beck CE, DeGroot J, Geary DF, Sklansky DJ, Freedman SB Comparison of isotonic and hypotonic intravenous maintenance fluids: a randomized clinical trial. JAMA Pediatr. 2015; **169**(5):445–451pmid:25751673

14 McNab S, Duke T, South M, et al. 140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial. Lancet.

2015; **385**(9974):1190–1197. Published online December 1, 2014pmid:25472864
15 Upadhyay A, Jaber BL, Madias NE Incidence and prevalence of hyponatremia. Am J Med. 2006; **119**(7, suppl 1):S30–S35pmid:16843082
16 Carandang F, Anglemyer A, Longhurst CA, et al Association between maintenance fluid tonicity and hospital-acquired hyponatremia. J Pediatr. 2013; **163**(6):1646–1651pmid:23998517CrossRefPubMedGoogle Scholar
17 Saba TG, Fairbairn J, Houghton F, Laforte D, Foster BJ. A randomized controlled trial of isotonic versus hypotonic maintenance intravenous fluids in hospitalized children. *BMC Pediatr.* 2011; **11**: 82
18 Choong K, Arora S, Cheng J *et al.* Hypotonic versus isotonic maintenance fluids after surgery for children: A randomized controlled trial. *Pediatrics* 2011; **128**: 857– 66
19 Armon K, Riordan A, Playfor S, Millman G, Khader A; Paediatric Research Society. Hyponatremia and hypokalemia during intravenous fluid administration. Arch Dis Child 2008; 93(4):285-7.
20 Hasim, N.; Bakar, M.A.A.; Islam, M.A. Efficacy and Safety of Isotonic and Hypotonic Intravenous Maintenance Fluids in Hospitalised Children: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Children 2021, 8, 785
21. Fabrice Gankam Kengne, Guy Decaux, Hyponatremia and the Brain Kidney Int Rep. 2018 Jan; 3(1): 24–35. Published online 2017 Sep 1. doi: 10.1016/j.ekir.2017.08.015
PMCID: PMC5762960
22 Moritz, Michael L., and Juan C. Ayus. "Maintenance intravenous fluids in acutely ill patients." *New England Journal of Medicine* 373.14 (2015): 1350-1360.
23 Feld, L.G.; Neuspiel, D.R.; Foster, B.A.; Leu, M.G.; Garber, M.D.; Austin, K.; Basu, R.K.; Conway, E.E., Jr.; Fehr, J.J.; Hawkins, C.; et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics 2018, 142, 1–12.
24 Zieg J[1] **(Leonard) Clinical Practice Guideline: Maintenance Intravenous Fluids in Children**
Leonard G. Feld, Daniel R. Neuspiel, Byron A. Foster, Michael G. Leu, Matthew D. Garber, Kelly Austin, Rajit K. Basu, Edward E. Conway, James J. Fehr, Clare Hawkins, Ron L. Kaplan, Echo V. Rowe,

Muhammad Waseem, Michael L. Moritz and SUBCOMMITTEE ON FLUID AND ELECTROLYTE THERAPY

25 Kutty N, John TB. Fluids' Safety in Children: Less Water or More Salt? Where does the truth lie?. *Oman Med J.* 2010;25(2):67-69. doi:10.5001/omj.2010.23