

**MAINTENANCE INTRAVENOUS FLUID IN HOSPITALIZED CHILDREN: A
RANDOMIZED, DOUBLE BLIND, CONTROLLED TRIAL OF 0.9%
NACL/DEXTROSE 5% VS. 0.45% NACL/DEXTROSE 5%**

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BACKGROUND AND HYPOTHESES

A.i. Research Problem: There are currently no standardized guidelines for the administration of maintenance saline IV fluids for hospitalized children at Sick Kids or in the literature. This will be the first prospective trial comparing hypotonic versus isotonic intravenous (IV) maintenance fluids in children. Additionally we will generate pilot data which will form the basis for an external grant proposal for a large scale randomized clinical trial to definitively examine the question of the most appropriate tonicity for paediatric IV maintenance solutions. Such a study would require a dichotomous outcome measure (dysnatremia: yes vs no). Given a baseline occurrence rate estimated at less than 10% in those receiving hypotonic fluids, over 1000 patients would be required. The impact and significance of our work is that it has the potential to guide the choice of IV maintenance fluids used in children internationally to decrease the morbidity and mortality currently seen as a result of dysnatremias in these children.

Hyponatremia, has become increasingly recognized as a cause of morbidity and mortality in hospitalized children.^{1,2,3,4,5,6} The main etiology of hyponatremia in these children has been attributed to the use of hypotonic maintenance IV fluids.^{3,5,6,7} The traditional practice of providing IV maintenance solutions containing 20-30 mmol/L of Na is based on “physiological needs” proposed by Holliday and Segar⁸ in 1957, derived from studies of 61 adults and children. The presence of non-physiologic ADH secretion in the great majority of hospitalized children

due to nausea, stress, pain, and surgical interventions, has confirmed that Holliday and Segar's recommendations are frequently inappropriately applied. The routine solution chosen for maintenance IV fluids in children varies widely amongst groups of physicians at the same hospital and between hospitals. The need for a controlled study to compare the outcomes using hypotonic and isotonic saline has been emphasized.^{9,11} To avoid the development of hyponatremia, it has been suggested that isotonic 0.9% NaCl/dextrose 5% should be the standard maintenance IV solution.^{3,5,7,9} The routine use of an isotonic maintenance fluid solution has not yet been studied, and concerns exist regarding the potential for hypernatremia and salt and water overload.¹⁰ An imminent IV fluid policy change at The Hospital for Sick Children will mandate that isonatremic (plasma Na=135–145 mmol/L) children receive fluid with a Na concentration of between 77 and 154 mmol/L. If isotonic solutions are to be recommended routinely, their overall safety, and specifically the occurrence of dysnatremias and volume overload, should be evaluated in a controlled prospective trial.

A.iv. Hypotheses: Compared with those who receive a hypotonic solution (0.45% NaCl/dextrose 5%), those who receive an isotonic solution (0.9% NaCl/dextrose 5%) will:

- a) Have a higher mean serum Na 48 hours after the initiation of IV maintenance fluids.
- b) Experience hyponatremia less frequently.
- c) Not experience a clinically significant Na increase or symptoms due to fluid overload.

(Note: Study is powered to detect difference in mean Na, not occurrence of dysnatremias)

B: OBJECTIVES

B.i. Primary: To compare the mean serum sodium at 48 hours⁵ following the initiation of therapy [or at study termination (see below)] with either 0.45% NaCl/dextrose 5% or 0.9% NaCl/dextrose 5%, in children requiring maintenance IV fluid administration.

B.ii. Secondary: To compare the following factors between the two groups:

- a) The number of children developing clinically significant hyponatremia (plasma Na<135 mmol/L with a drop of ≥ 4 mmol/L from baseline) or hypernatremia (plasma Na>145 mmol/L in conjunction with an increase of ≥ 4 mmol/L from baseline).
- b) Mean and percent change in weight from baseline.
- c) Proportion developing hypertension (>95th percentile for age and sex¹²).
- d) Proportion with clinically significant edema (see definition below).

C. RESEARCH DESIGN AND METHODOLOGY

C.i. Eligibility criteria. The study population will include children aged 1 month to 18 years, with an anticipated hospitalization ≥ 48 hours. Initial plasma Na must be between 135-145 mmol/L, with a management plan (determined by the responsible physician) to include IV fluids at $\geq 80\%$ and $\leq 120\%$ of maintenance. Blood work within 12 hours of initial patient contact by a member of the research team will act as baseline. For children who have had an IV saline bolus, the bolus may be pre- or post baseline bloods, as long as there is a 12 hour or less baseline blood.

Children will be excluded from study participation if they are diagnosed with, or clinically suspected to have, any of the following: dehydration/gastroenteritis, heart or liver failure, severe anemia (Hb<60 g/L), portal hypertension with ascites, metabolic disease, SIADH, diabetes insipidus or mellitus, hypertension, adrenal insufficiency, renal failure [creatinine>100 $\mu\text{mol/L}$

(< 3 years); >150 $\mu\text{mol/L}$ (≥ 3 years)], nephritic or nephrotic syndrome, Kawasaki disease, Sickle cell disease if requiring hyperhydration. Additionally children will be excluded if they are clinically edematous, if they are on diuretic medications, if their plasma glucose is >15 mmol/L, or if they require CCU admission.

Any patients requiring IV maintenance therapy having conditions/diseases not listed as excluded are eligible to be in this study. Examples include, but not limited to, pneumonia, bronchitis, asthma, sepsis, urinary tract infection, cellulites, osteomyelitis, feeding problems, aspiration, abdominal pain, and other miscellaneous conditions.

All children fitting the criteria outlined above will be identified from the Emergency Department and on inpatient wards by the clinical research coordinator in conjunction with the nursing staff on those units. Eligible patients will be identified by the study coordinator. For patients who present during the day, the coordinator will be contacted by ward staff. In order to capture patients who present after hours, the coordinator will review the list of patients who have been admitted from the Emergency Department on a daily basis. Patients who meet eligibility criteria will be approached by their responsible nurse or physician to discuss participation in this study. If they agree, one of the study investigators or a qualified designate will explain study requirements to the patient and/or their primary caregiver(s).

Consent will be obtained and children will be enrolled by one of the study investigators or by a qualified designate. We anticipate that the bulk of the study population will be enrolled in the ED and admitted to the Pediatric Medicine wards. The Emergency Department has 3000 admissions per year (or approximately 8.2 per day), therefore it is conservatively estimated that 1 patient/day will meet eligibility criteria and will agree to participate in this study.

C.ii. Study design: A randomized, double blind, controlled trial will be conducted comparing maintenance IV solutions with Na concentrations of 77 mmol/L (0.45% NaCl/dextrose 5%) and 154 mmol/L (0.9% NaCl/dextrose 5%) respectively. Blinding will be performed through the Pharmacy department which will randomly assigned a fluid type for each patient, stratifying subjects according to age (with a cut-off of 2.5 years) into strata A (patients less than or equal to 2.5 years of age) and Strata B (subjects with greater than 2.5 years of age) If serum potassium levels are 0.5 mmol/L or greater below the upper limit of normal for age (see Table 1 below), pharmacy will dispense the solution with 20mEq KCl/L of potassium included (either 0.45%NaCl with KCl 20mmol/L or 0.9%NaCl with KCl 20mmol/L, as randomized by Pharmacy), and the K result will be sent to the pharmacist at time of ordering study drug.

Table 1: Normal Potassium Ranges by Age in Children

Age range	Upper limit K (mmol/L)	Add potassium
1-5 months	3.5-5.6	$K \leq 5.1$
6-11 months	3.5-6.0	$K \leq 5.5$
1-15 years	3.7-5.0	$K \leq 4.5$
>16 years	3.7-4.8	$K \leq 4.3$

Maintenance fluid volume will be calculated using the Holliday-Segar formula⁸ (standard of care): Total daily fluid infusion equal to 100 mls/kg/day for children weighing ≤ 10 kg, 1000 mls + 50mls/kg for those weighing 10 to 20 kg, and 1500 mls +20 mls/kg for those >20 kg. This total will be divided by 24 to provide the hourly infusion rate. In patients taking oral fluids, the responsible team will be encouraged to decrease the IV rate accordingly (standard of care).

C.iii. Monitoring: Over the first 48 hours⁵ of their admission:

- a) Plasma urea, creatinine, glucose, total CO₂ and electrolytes will be checked at the time of IV start and every 24 hours thereafter (standard of care).
- b) Oral fluid intake (type and quantity) will be recorded and monitored by the CRNC.
- c) Daily weights will be obtained every 24 hours utilizing the same scale and clothing.
- d) Standardized clinical assessment of edema every 24 hours (by single pressure applied firmly for 5 seconds to a distal lower extremity and the lumbo-sacral region).
- e) Blood pressure will be monitored every morning by the study coordinator with the help of the patient's primary nurse.

C.iv. Study termination: A data safety monitoring committee will review the data after 35 patients as it relates to safety. Each patient's study period will terminate at either 48 hours from enrollment (primary endpoint), or when any of the following criteria appear:

- a) Plasma Na >145 mmol/L or <135 mmol/L with change of ≥ 4 mmol/L from baseline Na.
- b) Weight gain of >10% body weight compared with admission weight.
- c) Increased BP >20% diastolic or systolic compared with baseline on 3 consecutive readings over 1-2 hours and >95thile for age.

After study termination, a patient's IV solution will be chosen based on the best standard of care by the primary physician.

At any time during the study, emergency unblinding can be requested by the responsible physician/delegate if there are serious clinical concerns (e.g. significant hypernatremia or hyponatremia) when the treatment of the patient will be different by knowing which IV study

solution the patient is on. Whenever possible this should be discussed between the principal investigator and the responsible physician prior to requesting unblinding.

C.v. Sample Size: The primary outcome measure will be analyzed as a continuous variable. Sample size calculations are based on a two-sided α of 0.05 and power of 0.90. The effect size for the clinically important difference in the mean serum Na between the two groups is 2.5 mmol/L based on previous research¹³. Additionally, expert opinion is that this is the minimum clinically meaningful difference. The required sample size is 62 given a standard deviation of 3 mmol/L¹³.

Sample size adjustments: As there are multiple reasons why data may not be available (e.g. discharge prior to 48 hours, parental desire), we will estimate a 25% loss to follow-up, withdrawals, and missing data. Thus the final sample size will be 110.

C.vi. Data Analyses: All analyses will be undertaken by the intention to treat principle, except for adverse events, which will use the “as treated” principle.

Baseline variables: Baseline characteristics such as age at randomization, weight, and serum chemistry results will be compared between randomization groups using descriptive statistics. Frequency counts and percentages will be given for discrete variables, and means, medians, standard deviations and interquartile ranges for continuous variables. Baseline characteristics will be analyzed to determine if there is a need to adjust for any significant differences between the study groups.

Outcome variables: All statistical tests will be two-sided and will be conducted using the SAS system. The primary outcome, will be analyzed utilizing a 2-sample-t-test. Linear regression

methods will be used to investigate potential covariates (e.g. age, baseline Na, length of stay, presence of pain, vomiting, post-operative patient).

D. Adverse Events and Quality Assurance

Keeping in mind the outcome measures for this study, expected or potential risks/adverse events as a result of participation include dysnatremia, edema (weight gain), hypervolemia (fluid retention), and/or increase in blood pressure.

D.1 Definitions: An adverse event is any new, undesirable medical occurrence or change (worsening) of an existing condition in a subject that occurs during treatment (through completion of the end-of-study procedures), whether or not considered to be product related. Therefore, adverse events are treatment emergent signs or symptoms. In general, abnormal laboratory findings that are collected elsewhere on case report forms should not be recorded as adverse events; however, any associated clinical events should be reported as adverse events. Thus, only abnormal laboratory values that are associated with clinical sequelae should be recorded as adverse events.

A serious adverse event is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator's opinion on the relationship to study drug.

This includes, but may not be limited to, any event that (at any dose):

- is fatal
- is life-threatening (places the subject at immediate risk of death)
- requires hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

Important medical events may be considered serious that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject, require intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples include allergic bronchospasm, convulsions, and blood dyscrasias.

D.ii Adverse Event Reporting: All adverse events will be reported to the Hospital for Sick Children Research Ethics Board according to the Hospital for Sick Children's adverse event reporting requirements. All serious, unexpected adverse drug reactions to the study medication will be reported to Health Canada within 15 calendar days or for death or life-threatening events, within 7 calendar days. In the latter case, a follow-up report must be filed within 8 calendar days. Adverse reactions will be managed according to the Hospital for Sick Children's standard clinical management practices.

D.iii Quality & Safety Assurance: This project will be monitored by the Hospital for Sick Children (SickKids) Clinical Research Continuing Review program during the data collection phase of the project. The aim of Continuing Review is to ensure that all SickKids researchers are maintaining the highest ethical, scientific and safety standards for all study participants, and are in compliance with all relevant SickKids policies, provincial and federal legislation, and international guidelines such as ICH- Good Clinical Practice. All studies are categorized according to the Continuing Review Matrix based on the type of study and the level of risk (I to IV) to research subjects. This study is a Clinical Trial, Level II Risk. Thus the Clinical Research Monitor will review 10% of the research subjects' records for study eligibility, informed consent, adherence to study protocol, reporting of adverse drug reactions and adverse events, and data

quality including computer database security and storage of records. Findings of the Continuing Review will be presented to the Research Ethics Board and lead PI in a written report, and specific recommendations arising from the report will be implemented in a timely manner.

References

1. Moritz ML, Manole MD, Bogen DL, Ayus JC. Breastfeeding-associated hypernatremia: are we missing the diagnosis? *Pediatrics* 2005; **116**: e343-7.
2. Moritz ML, Ayus JC. Disorders of water metabolism in children: hyponatremia and hypernatremia. *Pediatr Rev* 2002; **23**: 371-380.
3. Moritz ML, Ayus JC. Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. *Pediatrics* 2003; **111**: 227-330.
4. Moritz ML, Ayus JC. Hospital-acquired hyponatremia: why are there still deaths? *Pediatrics* 2004; **113**:1395-1396.
5. 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**: 1279 –1284.
6. Choong K, Kho ME, Menon K, Bohn D. Hypotonic versus isotonic saline in hospitalised children: a systematic review. *Arch Dis Child* 2006; **91**: 828-835.
7. Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. *Pediatr Nephrol* 2005; **20**: 1687-1700.
8. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. *Pediatrics* 1957; **19**: 823-832.
9. Bianchetti MG, Bettinelli A. Differential diagnosis and management of fluid, electrolyte and acid-base disorders. *Comprehensive Pediatric Nephrology*. Eds Geary and Schaefer, Elsevier, Philadelphia, 2007 (In Press).
10. Holliday MA. Isotonic saline expands extracellular fluid and is inappropriate for maintenance therapy. *Pediatrics* 2005; **115**: 193-194.
11. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: Facts, fashions and questions. *Arch Dis Child* 2006; [Epub ahead of print].
12. Rosner B, Prineas RJ, Loggie JMH, Daniels SR. Blood pressure nomograms for children and adolescents by height, sex, and age in the United States. *J Pediatrics* 1993; **123(6)**: 874
13. Neville KA, Verge CF, Rosenberg AR, O' Meara MW, Walker JL. Isotonic is better than hypotonic saline for intravenous rehydration of children with gastroenteritis: a prospective randomized study. *Arch Dis Child* 2006; **91**: 226-232