Comparison of Isotonic and Hypotonic Intravenous Maintenance Fluids
A Randomized Clinical Trial

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IMPORTANCE Use of hypotonic intravenous fluids for maintenance requirements is associated with increased risk of hyponatremia that results in morbidity and mortality in children. Clinical trial data comparing isotonic and hypotonic maintenance fluids in nonsurgical hospitalized pediatric patients outside intensive care units are lacking.

OBJECTIVE To compare isotonic (sodium chloride, 0.9%, and dextrose, 5%) with hypotonic (sodium chloride, 0.45%, and dextrose, 5%) intravenous maintenance fluids in a hospitalized general pediatric population.

DESIGN, SETTING, AND PARTICIPANTS In this double-blind randomized clinical trial, we recruited 110 children admitted to a general pediatric unit of a tertiary care children's hospital from March 1, 2008, through August 31, 2012 (age range, 1 month to 18 years), with normal baseline serum sodium levels who were anticipated to require intravenous maintenance fluids for 48 hours or longer (intent-to-treat analyses). Children with diagnoses that required specific fluid tonicity and volumes were excluded.

INTERVENTIONS Patients were randomized to receive isotonic or hypotonic intravenous fluid at maintenance rates for 48 hours.

MAIN OUTCOMES AND MEASURES The primary outcome was mean serum sodium level at 48 hours. The secondary outcomes were mean sodium level at 24 hours, hyponatremia and hypernatremia, weight gain, hypertension, and edema. Confounding variables were included in multiple regression models. Post hoc analyses included change from baseline sodium level at 24 and 48 hours and subgroup analysis of children with primary respiratory diagnosis.

RESULTS Of 110 enrolled patients, 54 received isotonic fluids and 56 received hypotonic fluids. The mean (SD) sodium level at 48 hours was 139.9 (2.7) mEq/L in the isotonic group and 139.6 (2.6) mEq/L in the hypotonic group (95% CI of the difference, −0.94 to 1.74 mEq/L; P = .60). Two patients in the hypotonic group developed hyponatremia, 1 in each group developed hypernatremia, 2 in each group developed hypertension, and 2 in the isotonic group developed edema. Mean (SD) change from baseline to 48-hour sodium level was +1.3 (2.9) vs −0.12 (2.8) mEq/L, respectively (absolute difference, 1.4 mEq/L; 95% CI of the difference, −0.01 to 2.8 mEq/L; P = .05).

CONCLUSIONS AND RELEVANCE Our study results support the notion that isotonic maintenance fluid administration is safe in general pediatric patients and may result in fewer cases of hyponatremia.

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Hyponatremia is an increasingly recognized cause of morbidity and mortality in hospitalized children. The provision of hypotonic intravenous (IV) maintenance fluids is based on work from the 1950s that outlines the fluid and electrolyte requirements in healthy children based on energy expenditure and milk composition. Hypotonic IV maintenance fluids have generally remained the standard of care. Despite this increasing body of evidence, a multi-institutional survey conducted in the United Kingdom revealed that 78% of children receiving IV maintenance fluids were administered hypotonic fluids. A survey of US pediatric residents similarly revealed that 78% routinely prescribe hypotonic IV maintenance fluids. The reasons for the continued use of hypotonic IV maintenance fluids are unclear but may be explained in part by the lack of studies of hospitalized nonsurgical children outside the intensive care unit (ICU) setting.

To avoid the development of hyponatremia, it has been suggested that isotonic replace hypotonic fluids as the standard maintenance IV fluid. However, concerns have been raised that isotonic fluids may result in hypernatremia and fluid overload, and their use in blinded clinical trials in children outside the ICU or postoperative period has not been studied.

Our objective was to compare isotonic (sodium chloride, 0.9%, and dextrose, 5%) with hypotonic (sodium chloride, 0.45%, and dextrose, 5%) IV maintenance fluids in a hospitalized general pediatric population. We hypothesized that, in children administered an isotonic fluid compared with those given a hypotonic fluid, the former group would have a higher mean serum sodium level 48 hours after the initiation of IV maintenance fluid administration. We additionally hypothesized that children administered an isotonic fluid would be less likely to develop hyponatremia without developing clinically significant serum sodium increases or symptomatic fluid overload.

Methods

Patients

Eligible children aged 1 month to 18 years were initially evaluated in the emergency department (ED) of The Hospital for Sick Children (Toronto, Ontario, Canada) from March 1, 2008, through August 31, 2012, and were deemed to require admission to the general pediatric unit. On admission, families of eligible children were approached to discuss study participation; if they agreed, a study investigator (J.N.F., C.E.B., or D.J.S.) or qualified designate obtained written informed consent from the caregivers and participant assent when appropriate. Enrollment occurred Monday through Friday during daytime hours when a dedicated research assistant was available. The Hospital for Sick Children’s Research Ethics Board approved the study. The trial protocol can be found in the Supplement.

Participants had a normal initial serum sodium level (135-145 mEq/L) to convert to millimoles per liter, multiply by 1), a management plan that included IV fluid administration at 80% to 120% of maintenance as defined by the Holliday-Segar method, and an anticipated requirement for IV fluids of 48 hours or longer. Children diagnosed as having or clinically suspected of having any of the following were excluded because these conditions usually have specific fluid requirements: dehydration with ongoing fluid losses; cardiac, renal, or hepatic failure; hemoglobin level less than 6 g/dL (to convert to grams per liter, multiply by 10); portal hypertension with ascites; metabolic disease; diabetes insipidus or mellitus; hypertension; adrenal insufficiency; nephritic or nephrotic syndrome; and Kawasaki disease. Children were also excluded if they were edematous, were taking diuretic medications, had a serum glucose level greater than 270 mg/dL (to convert to millimoles per liter, multiply by 0.0555), or required ICU care. Children remained eligible if they received an IV bolus of an isotonic fluid before enrollment as long as they were considered euvolemic and only required IV maintenance fluids with no additional rehydration after enrollment.

Randomization and Blinding

Master randomization tables were prepared and held by the institution’s Research Support Pharmacy. Patients were allocated in a 1:1 ratio to treatment with a maintenance IV fluid that contained 154 mEq/L of sodium (sodium chloride, 0.9%, and dextrose, 5%) or 77 mEq/L of sodium (sodium chloride, 0.45%, and dextrose, 5%), respectively. The randomization sequence was computer generated, using balanced blocks of 4 and stratified by age (<2.5 vs ≥2.5 years). The randomization code remained secure until enrollment and data entry were complete. Blinding was accomplished by the placement of an opaque amber plastic sleeve over the 1-L study IV fluid bags by the research pharmacist before its dispensing. This process enabled us to conceal the identity of the IV fluid from the patient, family, nurses, physicians, and research team.

Patients taking oral fluids before the 48-hour study end point had their IV rate reduced to aim for a total fluid intake in keeping with standard total daily maintenance fluid volumes (ie, Holliday-Segar method). Potassium was ordered as 0, 20, or 40 mEq/L as entered by the responsible physician into a computer physician order entry system. This procedure enabled the Research Support Pharmacy to add the potassium requested before distribution to the inpatient unit.

Monitoring

Serum sodium, potassium, chloride, urea, creatinine, glucose, and total carbon dioxide were measured at the time of IV fluid administration and subsequently every 24 hours. Blood was drawn by peripheral venous sampling. All sodium measurements were performed by the hospital clinical laboratory using the VITROS 5600 integrated system (Ortho-Clinical Diagnostics) with an SD of 0.7 mEq/L and coefficient of varia-
Intravenous Maintenance Fluids

Primary Outcome
The primary outcome was mean serum sodium level 48 hours after initiation of therapy. This outcome was selected because dysnatremias are too uncommon to study with this design. Mean serum sodium level could enable the identification of a trend toward dysnatremia development and could potentially justify the conduct of very large studies that focused on clinically significant hyponatremic and hypernatremic events. Confounding variables, including age and baseline sodium level, were identified a priori and placed into a multiple regression model for analysis.

Secondary Outcomes
Secondary outcomes included the following: (1) mean serum sodium level 24 hours after initiation of therapy; (2) development of hyponatremia, defined as serum sodium level less than 135 mEq/L associated with sodium decrease of 4 mEq/L or more from baseline; (3) development of hypernatremia, defined as serum sodium level greater than 145 mEq/L associated with sodium increase of 4 mEq/L or more from baseline; and (4) signs of fluid overload a priori defined as any of the following: mean and percent change in weight from baseline (increase >10% from weight at admission), development of hypertension (increase >20% diastolic or systolic compared with baseline), or edema.

We performed a post hoc subgroup analysis based on presenting diagnosis, comparing only those children with a primary respiratory diagnosis (eg, pneumonia, asthma, or bronchiolitis). We also performed a post hoc analysis calculating the mean change from baseline to 24- and 48-hour serum sodium levels between the 2 groups.

Sample Size
Enrolling 110 children would provide 90% power to detect a 2.5-mEq/L difference in mean serum sodium levels at 48 hours given a 2-sided type I error probability of .05 and an SD of 3 mEq/L. The minimal important difference was selected based on expert opinion, biochemical accuracy, and previous studies. Our sample size calculation included a 25% adjustment for losses to follow-up, withdrawals, early termination, and missing data.

Statistical Analysis
All analyses were undertaken by the intent-to-treat principle except for adverse events, for which the as-treated principle was used. Analyses were performed with SAS statistical software, version 9.3 (SAS Institute Inc). To adjust for multiple testing, the .01 significance level was selected for secondary outcome measures.

Baseline characteristics were compared between randomization groups using descriptive statistics. Discrete variables were compared using frequency counts and percentages and continuous variables using means, medians, SDs, and interquartile ranges. If a nonnormal distribution was detected (through use of Q-Q plots), between-group comparisons used nonparametric tests.

An unadjusted 2-sample t test was used to examine the difference in the primary outcome between groups and subgroups and for the continuous, secondary outcome, 24-hour serum sodium levels. We used the Fisher exact test to examine the difference between groups for the dichotomous secondary outcomes of hyponatremia or hypernatremia and fluid overload. The 48-hour mean serum sodium levels were also analyzed using linear regression models. Potential covariates identified a priori were age and baseline serum sodium level, which were included in all regression analyses.

All adverse events were reported to the The Hospital for Sick Children Research Ethics Board according to the hospital’s adverse event reporting requirements. A data and safety monitoring committee reviewed the data after entry of 35 patients in a masked manner and evaluated all adverse events.

Results

Participants
Of the 186 potentially eligible children identified in the ED, 110 were enrolled (Figure). The median age was 4.5 years (range, 0.1-17.2 years). The most common diagnoses were pneumonia, sickle cell disease, infections, asthma, and vomiting (Table 1). No significant differences were found between the groups in terms of age, sex, baseline weight, baseline sodium level, or diagnoses. While participating in the study, patients in both groups received similar total volumes of IV and oral fluids (Table 1). There were no known compromises in the blinding procedures.

Primary Outcome
The mean (SD) 48-hour serum sodium level was 139.9 (2.7) mEq/L in the isotonic group and 139.6 (2.6) mEq/L in the hypotonic group (absolute difference, 0.3 mEq/L; 95% CI of the difference, −0.94 to 1.74 mEq/L; P = .60). After adjustment for a priori identified covariates, the 48-hour serum sodium levels did not differ significantly (95% CI of the difference, −2.0 to 0.57 mEq/L; P = .27) (Table 2).

References


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Secondary Outcomes
Mean (SD) serum sodium levels at 24 hours did not differ between the groups (140.5 [2.7] vs 139.6 [2.7] mEq/L, respectively; 95% CI of the difference, −0.22 to 2.02 mEq/L; \( P = .14 \)).

Two patients in the hypotonic group developed hyponatremia; both had serum sodium levels of 134 mEq/L after 24 hours and were terminated from the study. These patients included a child with pneumonia and a baseline sodium level of 141 mEq/L and a child with sickle cell disease who had a baseline sodium level of 138 mEq/L. One patient in each group developed hypernatremia with sodium levels of 147 mEq/L at 24 hours; these patients included a child in the isotonic group with bronchiolitis and an initial sodium level of 139 mEq/L and a child with asthma in the hypotonic group who had a baseline sodium level of 143 mEq/L (Table 2).

The change in weight between baseline and 48 hours did not differ between the groups. Two patients in each group developed hypertension, and 2 patients in the isotonic group developed edema.

Post Hoc Exploratory Analysis
The mean (SD) change from baseline to 48-hour sodium level was 1.9 (3.1) mEq/L in the isotonic group compared with −0.02 (3.1) mEq/L in the hypotonic group (absolute difference, 1.9 mEq/L; 95% CI of the difference, 0.6–3.1 mEq/L; \( P = .004 \)).

The subgroup analysis of children with a primary respiratory diagnosis revealed a mean change from baseline to 48-hour sodium level of 2.5 mEq/L (95% CI, 0.76–4.2 mEq/L) in the isotonic group compared with −0.21 mEq/L (95% CI, −1.8 to 1.4 mEq/L) in the hypotonic group (absolute difference, 2.7 mEq/L; 95% CI of the difference, 0.34–5.1 mEq/L; \( P = .05 \)) (Table 2).

Adverse Events
No significant adverse events were attributed to the study intervention. Two patients (1 from each group) required transfer to the ICU for increasing respiratory distress that was deemed to be unrelated to the volume and type of IV fluids administered. One patient in the isotonic group had a self-resolving episode of bradycardia of unknown origin.

Discussion
In a population of general pediatric patients outside the ICU, there was no significant difference in mean serum sodium levels at 24 and 48 hours between those administered isotonic or hypotonic IV maintenance fluids. Although our study was not powered to detect a statistical difference in any of the second-
ary outcomes, 2 of the 56 patients in the hypotonic group developed hyponatremia based on our a priori definition (vs nil in the isotonic group) and required study termination at 24 hours. Although they only had mild hyponatremia, we do not know how low their sodium level would have been at 48 hours if they had continued to receive hypotonic fluids.

Although patients receiving isotonic maintenance fluids had a small increase in serum sodium levels at 24 and 48 hours, these increases were not clinically significant; there were no increases in the numbers of children developing clinically relevant hypernatremia or fluid overload. One case of mild hypernatremia occurred in each study group. An equal number of patients in each group developed hypertension.

A post hoc analysis evaluating change in serum sodium from baseline found that children receiving isotonic fluids had increased their sodium level 1.9 mEq/L more than the hypotonic group at 24 hours and 1.4 mEq/L more at 48 hours. These differences are likely not clinically significant. A post hoc analysis on the subgroup of children with primary respiratory diagnoses revealed an increased absolute difference in sodium of 2.7 mEq/L from baseline to 48 hours, which is of questionable clinical significance.

The literature is currently lacking in high-quality studies comparing the effect of IV maintenance fluid tonicity on serum sodium levels in children admitted to a general pediatrics inpatient unit. Two systematic reviews in 2006 and 2007 on the use of IV maintenance fluids in hospitalized children identified a paucity of well-designed studies on which to base the selection of IV maintenance fluids. The identified studies focused on surgical populations and children with dehydration and reported that those administered hypotonic fluids developed lower serum sodium levels. Since the publication of these reviews, a number of studies addressing the issue of IV fluid tonicity and hyponatremia in children in the ICU and/or postoperative settings have been published.

Two meta-analyses published in 2014 reviewed randomized control trials that compared isotonic and hypotonic IV maintenance fluids in hospitalized children. Wang et al included 10 randomized control trials that involved 855 children; all except one involved ICU or postoperative children. They reported an increased risk of developing hyponatremia in children prescribed hypotonic maintenance fluids (so-

### Table 1. Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Isotonic Group (n = 54)</th>
<th>Hypotonic Group (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>3.9 (2.0-6.9)</td>
<td>5.8 (1.4-11.2)</td>
</tr>
<tr>
<td>Male sex</td>
<td>28 (51.9)</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Weight, median (IQR), kg</td>
<td>15.9 (11.3-23.4)</td>
<td>18.3 (9.6-35.7)</td>
</tr>
<tr>
<td>Baseline serum sodium, mean (SD), mEq/L</td>
<td>138.7 (2.5)</td>
<td>139.5 (2.6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (28)</td>
<td>13 (23)</td>
</tr>
<tr>
<td>Asthma</td>
<td>3 (6)</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>4 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>9 (17)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Infections*</td>
<td>5 (9)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (9)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Other*</td>
<td>13 (24)</td>
<td>18 (32)</td>
</tr>
<tr>
<td>Respiratory subgroup</td>
<td>22 (41)</td>
<td>21 (38)</td>
</tr>
<tr>
<td>IV fluid volume during study, mean (SD), mL/kg/h</td>
<td>2.5 (1.0)</td>
<td>2.3 (1.1)</td>
</tr>
<tr>
<td>Oral fluid intake, median (IQR), mL/kg/h</td>
<td>0.7 (0.1-1.7)</td>
<td>0.7 (0.2-1.2)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; IV, intravenous.

\* Data are presented as number (percentage) of patients unless otherwise indicated.

### Table 2. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Isotonic Group</th>
<th>Hypotonic Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>30</td>
<td>34</td>
<td>.60</td>
</tr>
<tr>
<td>Serum sodium at 48 hours, mean (SD), mEq/L</td>
<td>139.9 (2.7)</td>
<td>139.6 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>47</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Serum sodium at 24 hours, mean (SD), mEq/L</td>
<td>140.5 (2.7)</td>
<td>139.6 (2.7)</td>
<td>.14</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>2 (3.6)</td>
<td>.26</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>1 (1.9)</td>
<td>1 (1.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Weight change at 48 hours, mean (SD), kg</td>
<td>0.9(0.8)</td>
<td>0.2 (0.6)</td>
<td>.25</td>
</tr>
<tr>
<td>Weight change at 48 hours, mean (SD)</td>
<td>2.4 (4.4)</td>
<td>1.1 (2.5)</td>
<td>.23</td>
</tr>
<tr>
<td>Developed hypertension</td>
<td>2 (3.7)</td>
<td>2 (3.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Developed edema</td>
<td>2 (3.7)</td>
<td>0</td>
<td>.15</td>
</tr>
<tr>
<td>Post Hoc Exploratory Analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in sodium from baseline to 48 hours, mean (SD), mEq/L</td>
<td>1.3 (2.9)</td>
<td>−0.12 (2.8)</td>
<td>.05</td>
</tr>
<tr>
<td>Change in sodium from baseline to 24 hours, mean (SD), mEq/L</td>
<td>1.9 (3.1)</td>
<td>−0.02 (3.1)</td>
<td>.004</td>
</tr>
</tbody>
</table>

### Respiratory Diagnosis Subgroup

| Change in sodium from baseline to 48 hours, mean (SD), mEq/L | 2.5 (1.7) | −0.21 (1.6) | .05     |

Abbreviations: IQR, interquartile range; IV, intravenous.

\* Data are presented as number (percentage) of patients unless otherwise indicated.
dium <136 mEq/L; relative risk, 2.24; 95% CI, 1.52-3.31) and also of developing severe hyponatraemia (sodium <130 mEq/L; relative risk, 5.29; 95% CI, 1.74-16.06). In keeping with our findings, the mean sodium level in children after receiving hypotonic fluids was lower than in those who received isotonic fluids (−2.09 mEq/L; 95% CI, −2.91 to −1.28 mEq/L), and no difference was found between the 2 interventions in the risk of hyponatraemia (relative risk, 0.73; 95% CI, 0.22-2.48).

The other meta-analysis29 included an additional 2 randomized clinical trials. Two-thirds of the patients included were postoperative surgical patients, and half of the studies were conducted in ICUs. In keeping with the aforementioned review, this review by Foster et al29 reported an increased risk of hyponatraemia in those receiving hypotonic IV maintenance fluids and no differences in the secondary outcomes for hyponatraemia and signs of fluid overload (eg, hypertension and edema). The authors list among the limitations a lack of studies looking at sodium chloride, 0.45% vs 0.9%, in nonoperative and non-ICU patients and the use of brief (24 hours) end points. The latter point is crucial because longer follow-up periods could potentially reveal higher rates and more clinically significant episodes of dysnatremia. Our study provides results that will help address both these deficiencies.

The many studies performed in the last decade and analyzed in the meta-analyses discussed above consistently suggest that, compared with hypotonic IV maintenance fluids, isotonic fluids decrease the risk of developing hyponatraemia without increasing the risk of fluid overload and hyponatraemia. However, these studies focus on children who are critically ill in an ICU or who have just undergone a surgical operation. Thus, these results are not necessarily generalizable to children admitted to general medical wards.

Our study was powered to detect a difference in serum sodium levels at 48 hours of 2.5 mEq/L between the 2 groups. This difference, which was deemed to be the minimally clinically relevant outcome using sodium levels as a continuous variable, was selected based on a review of previous studies and expert opinion. To conclusively determine the risk of developing significant dysnatremias requires an extremely large sample size that will be challenging to achieve prospectively. Although a number of patients did not complete the full 48-hour study period, we were able to achieve our a priori desired sample size of children with complete data. We excluded children with conditions that require specific IV fluid prescriptions in terms of rate and tonicity (eg, those with dehydration requiring ongoing rehydration and/or replacement fluids); therefore, we cannot generalize our findings to such patients. Finally, our findings are not generalizable to children admitted to an ICU or those who have recently undergone surgery.

Conclusions

We found no clinically significant difference in our primary outcome of mean serum sodium level at 48 hours after IV fluid administration in general pediatric patients treated with isotonic or hypotonic maintenance fluids. There were, however, 2 cases of hyponatraemia in the hypotonic group at 24 hours. Our study results support the notion that isotonic maintenance fluid administration is safe in general pediatric patients and may result in fewer cases of hyponatraemia.

ARTICLE INFORMATION

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Author Contributions: Drs Friedman and Freedman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Friedman, Beck, Geary, Freedman. Acquisition, analysis, or interpretation of data: Friedman, Beck, DeGroot, Sklansky, Freedman. Drafting of the manuscript: Friedman, Freedman. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Friedman, Beck, DeGroot, Freedman. Obtained funding: Friedman, Beck, Freedman. Administrative, technical, or material support: DeGroot, Sklansky, Freedman. Study supervision: Friedman, Freedman. Conflict of Interest Disclosures: None reported.
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