Hypotonic versus Isotonic Fluids in Hospitalized Children: A Systematic Review and Meta-Analysis

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Objective To determine whether the use of hypotonic vs isotonic maintenance fluids confers an increased risk of hyponatremia in hospitalized children.

Study design A search of MEDLINE (1946 to January 2013), the Cochrane Central Registry (1991 to December 2012), Cumulative Index for Nursing and Allied Health Literature (1990 to December 2012), and Pediatric Academic Societies (2000-2012) abstracts was conducted using the terms "hypotonic fluids/saline/solutions" and "isotonic fluids/saline/solutions," and citations were reviewed using a predefined protocol. Data on the primary and secondary outcomes were extracted from original articles by 2 authors independently. Meta-analyses of the primary and secondary outcomes were performed when possible.

Results A total of 1634 citations were screened. Ten studies (n = 893) identified as independent randomized controlled trials were included. Five studies examined subjects in the intensive care unit setting, including 4 on regular wards and 1 in a mixed setting. In hospitalized children receiving maintenance intravenous fluids, hyponatremia was seen more often in those receiving hypotonic fluids than in those receiving isotonic fluids, with an overall relative risk of 2.37 (95% CI, 1.72-3.26). Receipt of hypotonic fluids was associated with a relative risk of moderate hyponatremia (<130 mmol/L) of 6.1 (95% CI, 2.2-17.3). A subgroup analysis of hypotonic fluids with half-normal saline found a relative risk of hyponatremia of 2.42 (95% CI, 1.32-4.45).

Conclusion In hospitalized children in intensive care and postoperative settings, the administration of hypotonic maintenance fluids increases the risk of hyponatremia when compared with administration of isotonic fluids. For patients on general wards, insufficient data are available based on the reviewed studies, and individual risk factors must be assessed. *(J Pediatr 2014;165:163-9)*.

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Approximately 2.2 million non-newborn children are admitted to the hospital every year in the US, many of whom receive maintenance intravenous (IV) fluids during their stay.[1,2] There is a long tradition of prescribing precise maintenance fluid therapy to provide appropriate amounts of water, glucose, and electrolytes for hospitalized children.[3,4] The volume of maintenance fluid is calculated using an adaptation of Holliday and Segar's work,[4] now known as the "4-2-1 rule." This calculation relies on the relationship between energy and body weight to calculate water needs. In addition to calculating the amount of water needed, Holliday and Segar created the maintenance fluid in a hypotonic solution to best approximate solute needs. However, we now understand that water regulation in sick children is affected by both osmotic and nonosmotic (ie, stress, infection) stimuli for increased antidiuretic hormone (ADH) production.[5,6]

Given our current understanding of fluid regulation, the composition of those fluids has been the subject of debate,[7-9] particularly regarding tonicity. The UK Royal College of Pediatrics has questioned the use of hypotonic fluids, issuing safety warnings regarding their use.[10] Nevertheless, a study showed that 78% of pediatric residents prescribed hypotonic fluids in hypothetical clinical situations in which the patient was at high risk for increased ADH secretion,[11] and thus at increased risk for hyponatremia.

When administering hypotonic fluids, a subset of children have a small but significant individual risk of hyponatremia and its sequelae, including brain swelling and death.[12] Given the extent of IV fluid use, calculating a population estimate of risk from this small individual risk allows estimation of the potential impact of this risk.

A meta-analysis by Choong et al[13] found a significant risk of developing hyponatremia using hypotonic fluids compared with isotonic fluids (OR, 17.22; 95% CI, 8.67-34.2). They showed consistency over multiple outcomes; however, their meta-analysis included both randomized and cohort studies. Multiple randomized, clinical trials have followed, primarily in postoperative and intensive care unit (ICU) patients.

ADH	Antidiuretic hormone
ICU	Intensive care unit
IV	Intravenous

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In the present study, we aimed to address the question of whether hypotonic saline vs isotonic saline infused at maintenance rates in hospitalized children confers an increased risk of developing hyponatremia, defined here as a serum sodium level <135 mmol/L.

Methods

We developed a detailed protocol for the selection of studies (available on request from the authors). Studies eligible for inclusion were clinical trials that enrolled hospitalized children aged 1 month to 18 years and compared isotonic and hypotonic IV fluids. Studies were excluded if they did not have a comparison group or only studied patients with diabetes insipidus, diabetic ketoacidosis, burns, or shock, because the former is known to involve sodium dysregulation and the latter 3 require disease-specific protocols for fluid management.

A search of MEDLINE (1946 to January 2013), Cochrane Central Registry (1991 to December 2012), CIANHL (1990 to December 2012), and PAS (2000-2012) abstracts was completed in January 2013. Terms used in the search were "hypotonic fluids/saline/solutions" and "isotonic fluids/saline/solutions," with the restrictions of children and clinical trial. The results from the initial search were cross-referenced and liberally screened by title. For the second round, 2 of the authors independently screened abstracts and full articles, as necessary, using the inclusion and exclusion criteria. Authors of unpublished or partially published studies that resulted from the search were contacted for further information. Two of the authors conducted independent hand searches of the reference lists of all selected full text articles. Only randomized controlled trials were included in the meta-analysis.

Our primary outcome was hyponatremia, defined as a serum sodium level <135 mmol/L with assessment at the longest time point for each study that did not exceed 24 hours. Secondary outcomes were change in serum sodium level from baseline, characterized as moderate hyponatremia (serum sodium <130 mmol/L) or severe hyponatremia (serum sodium <125 mmol/L). Adverse events of hypernatremia (serum sodium >145 mmol/L); edema; hypertension; neurologic complications, defined as new-onset systemic neurologic symptoms (eg, seizures, altered mental status); and mortality were assessed as well.

We collected data using a standardized form that was pilot tested by 2 of the authors. The authors of primary studies were contacted for clarification of results. Data extracted for each study included study date and duration; number and age of subjects enrolled and completed in each group; interventions compared, including fluid infusion rates and tonicity; setting (ICU vs ward); postoperative (surgical) or medical status; exclusion criteria and comorbidities of subjects; outcomes assessed and time points of data collection; and the primary and secondary outcomes as defined by this review. Hypotonic fluids were defined as tonicity <250 mmol/L for this review. Isotonic fluids were defined as normal (0.9%) saline, Ringer lactate, Hartmann solution, and any other fluid with tonicity approaching that of normal serum.

Using the criteria proposed by the Cochrane group,[14] we assessed each study in the final analysis for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Two authors independently graded these variables for each individual study as low, high, or unclear level of bias. An article with a high risk of bias was evaluated by reviewers for inclusion status in the final analysis. We assessed the risk of bias across studies, specifically publication bias, was assessed using a funnel plot with RevMan 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).[15]

We conducted a brief qualitative review of the contribution of the cohort studies excluded from the meta-analysis (**Table I**; available at www.jpeds.com). The purpose of this review was to determine whether outcomes differed significantly between the nonrandomized studies and the randomized clinical trials. Two authors extracted data independently as described above. For each study, we examined the study design and setting, subject characteristics, type of intervention or comparison, and outcome data related to serum sodium concentration.

Statistical Analyses

We used a random-effects model to report relative risk for the individual studies and the overall estimate of risk in the meta-analysis. We applied Mantel-Haenzel methods to estimate the combined relative risk estimate for dichotomous outcomes and inverse variance for the continuous outcome of change in serum sodium concentration using RevMan 5.2.[15] I^2 statistics were used to assess heterogeneity. We used the following equation to calculate the number needed to harm:

$$\text{number needed to treat} = 1/[\text{assumed control event rate} - (1 - \text{relative risk estimate})].^{14}$$

We used a range of values (5%-20%) from the published literature for the assumed control event rate of the primary outcome of hyponatremia.

Based on theoretical concerns regarding applicability between groups, we a priori defined subgroups for sensitivity analysis as postoperative surgical subjects vs nonoperative (ie, medical) subjects. After reviewing the trials for inclusion, we conducted a secondary sensitivity analysis of the risk for hyponatremia (ie, sodium <135 mmol/L) in patients receiving 1/2 normal saline (0.45%) vs those receiving isotonic fluid. The rationale for this approach was to examine more current practice, given that use of 0.5 normal 0.45% saline has become accepted practice,[11] and the amount of free water in 0.5 normal 0.45% saline is one-half that of 0.25 normal 0.225% saline, which can significantly affect the intervention.

Results

Our initial search identified 1634 articles, which, after cross-reference and initial screening, we narrowed to 85