

REVIEW ARTICLE

Hospital-Acquired Hyponatremia in Pediatric Patients: A Review of the Literature

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Hypotonic intravenous (IV) fluids in children are a mainstay of therapy based on a recommendation made in 1957 by Holliday and Segar. Since that time, hospital-acquired hyponatremia caused by hypotonic IV fluids has been found to be an additional risk factor in the cause of death and neurological impairment in acutely ill children. This article reviews and critically evaluates the literature regarding the association of hyponatremia and hypotonic IV fluids in pediatric hospitalized, postoperative, and critical care patients.

INDEX TERMS hyponatremia, hypotonic saline, intravenous fluids

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INTRODUCTION

Acute hyponatremia is defined as a decline in serum sodium (Na^+) to less than 136 mEq/L. Symptoms of hyponatremia include neurological dysfunction associated with cerebral edema with early signs of nausea, headache, and malaise. Hyponatremia can eventually lead to seizures and death depending on the magnitude and severity of onset.¹ Hospitalized and postoperative children are at high risk for developing acute hyponatremia because the early signs are nonspecific and health care providers could attribute these signs to other causes such as the present illness, postoperative effects, anesthesia, or opioids. Most instances of neurological dysfunction and deaths resulting from hyponatremic encephalopathy have occurred in surgical patients.²

The kidney is the main regulator of water through antidiuretic hormone (ADH). ADH acts directly on the kidneys causing reabsorption of water, which helps maintain normal Na^+ levels. When Na^+ levels decrease, ADH release is inhibited; this feedback system helps Na^+ levels remain within normal range even with varying electrolyte-free water intake and excretion. However, numerous nonosmotic stimuli can stimulate

ADH response. Some examples of nonosmotic stimuli include nausea, vomiting, pain, stress, trauma, and opioids. Hospitalized and postoperative children have multiple risk factors that predispose them to nonosmotic release of ADH, which will cause the retention of free water and could ultimately lead to acute hyponatremia.³

In 2009, the Institute for Safe Medication Practice (ISMP) warned against using hypotonic intravenous (IV) fluids in postsurgical pediatric patients. ISMP called for greater education of healthcare professionals about the causes, signs and symptoms that lead to acute hyponatremia. They also recommend that standards of practice should be established for postoperative IV fluids in children.³

This ISMP warning was prompted by the reports of deaths of 2 pediatric patients resulting from acute hyponatremia.³ The first case was that of a 4-year-old child who underwent a tonsillectomy as day surgery and the second case was that of a previously healthy 3-year-old child who presented to the emergency department (ED) with a 1-day history of nausea and vomiting. Neither patient had a significant medical history or laboratory value abnormalities. Both patients received large volumes of IV fluids, and 1 patient received hypotonic IV fluids. Both of the children

experienced incontinence and lethargy and had Na^+ concentrations less than 120 mEq/L. Both children also each experienced a seizure and cerebral edema with brain herniation secondary to acute hyponatremia.

This article reviews and evaluates the current literature regarding the association between hyponatremia and hypotonic IV fluids in pediatric hospitalized, postoperative, and critical care patients.

METHODS

We searched PubMed (2006-2012) and MEDLINE (2006-2012), using the terms "hypotonic solutions," isotonic solutions," "fluid therapy," and synonyms or related terms. We reviewed the reference lists of all identified studies and reviews. We decided to include only articles after 2006, as Choong et al¹¹ published a review article in that year. We included controlled trials and cohort and case-control studies in pediatric patients hospitalized for any medical or surgical condition who received interventions with hypotonic (sodium content < normal saline [NS] or lactated Ringer [LR] solution) or isotonic (NS or LR) IV fluids. Surveys and review articles were not included in this article. We identified 11 studies that met the inclusion criteria were evaluated in this article (Table).

LITERATURE REVIEW

Hypotonic Saline Solutions

Hypotonic IV fluids in children are used based mainly on a recommendation made by Holliday and Segar⁴ in 1957. However, since that time, hypotonic IV fluids have been shown to cause hyponatremia. Hospital-acquired hyponatremia caused by hypotonic IV fluids administration has been found to be a primary risk factor in the cause of death and neurological impairment from hyponatremic encephalopathy.² Armon et al⁵ conducted a cross-sectional survey, including 17 hospitals in the United Kingdom, which found that 77 of 99 hospitalized children (78%) were receiving hypotonic saline IV fluids. Baseline serum electrolyte values were collected only in 79% of the patients. Twenty-one of the 86 patients had Na^+ concentrations that were hyponatremic ($\text{Na} < 135$ mEq/L), and 4 of those patients had Na^+ concentrations less than 130 mEq/L. Fif-

teen patients (71%) were receiving hypotonic solution, and 6 (28%) received more than 120% of the calculated maintenance rate. The authors concluded that fluids should be used with the same degree of caution given to other drugs, with careful regard to volume and tonicity and with appropriate serum electrolyte monitoring.

Hanna and Saberi⁶ conducted a retrospective study to examine incidences of hyponatremia after patients had been given hypotonic saline IV fluids. One hundred twenty-four patients who were previously healthy, ages 1 month to 12 years old, who were admitted to the hospital for acute gastroenteritis and dehydration and who had at least two Na^+ concentrations assessed (1 patient on admission and 1 at 4 and 24 hours afterwards) were included. Upon admission, 97 patients were isonatremic, 19 patients were mildly hyponatremic (Na 130-134 mEq/L), and 8 were mildly hypernatremic (Na 146-150 mEq/L). Following IV fluid administration with hypotonic solution at maintenance rate or maintenance plus deficit, 99 patients were isonatremic, 23 patients were hyponatremic, and 2 patients were hypernatremic ($p=0.34$). Eighteen of 97 patients (18.5%) with isonatremia on admission developed hyponatremia ($p<0.005$). The incidence of acquired hyponatremia was similar in patients on maintenance rate or maintenance plus deficit hypotonic IV fluids ($p=0.60$). There was a rise in the Na^+ concentration only in patients who were hyponatremic upon admission; all other patients experienced a decline in Na^+ . The authors were unable to detect a relationship between the type of IV fluids or the rate of administration and the incidence of hyponatremia. They concluded that prolonged use of hypotonic IV fluids may have the potential to cause acute hyponatremia in children with gastroenteritis and dehydration.

A prospective observational study evaluated the incidence of hospital-acquired hyponatremia in postoperative children receiving hypotonic saline.⁷ Seventeen of 81 patients (21%) developed hyponatremia ($\text{Na} \leq 135$ mEq/L) at 12 hours (95% confidence interval [CI], 3.7-38.3) and 15 of 48 patients (31%) developed hyponatremia at 24 hours (95% CI, 11.4-50.6). No patients developed Na^+ concentrations less than 130 mEq/L or had neurological adverse effects or died. This study showed that the incidence of hyponatremia in postoperative children receiving hypotonic saline solutions is high and progresses over time

Table. Summary of the Literature

Author	Patient Population	No. of patients	Study Conclusion(s)
Armon et al ⁵	Hospitalized patients; 7 days–16 yrs of age	99	Fluids should be used with the same degree of caution that is given to other drugs with careful regard to volume and tonicity and appropriate electrolyte monitoring
Hanna and Saberi ⁶	Hospitalized patients with gastroenteritis; 1 month–12 yrs of age	124	Unable to detect a relationship between the type of IV fluids or rate of infusion and the development of hyponatremia
Eulmesekian et al ⁷	Postoperative PICU patients	81	The incidence of hyponatremia in postoperative PICU children receiving hypotonic saline was high and progressive over time
Kannan et al ⁸	Hospitalized patients; 3 months–12 yrs of age	167	NS at maintenance rate reduces the incidences of hospital-acquired hyponatremia
Yung and Keeley ⁹	PICU patients; 11 months–16 yrs of age	50	Surgical patients had a greater fall in Na ⁺ concentrations than medical patients. Fluid type had a greater effect on Na ⁺ concentration than fluid rate
Neville et al ¹⁰	Postoperative patients; 6 months–15 yrs of age	124	Fluid type was more important than fluid rate in the prevention of hyponatremia. Isotonic saline emerged as protective and 50% maintenance rate emerged as potentially deleterious in the development of hyponatremia
Choong et al ¹¹	Elective surgery patients; 6 months–16 yrs of age	258	Isotonic IV fluids are safer than hypotonic IV fluids in protecting against acute postoperative hyponatremia
Saba et al ¹²	Medical and postoperative surgery patients; 3 months–18 yrs of age	37	Hypotonic IV fluids administration during the first 12 hr did not result in a drop of Na ⁺
Au et al ¹³	Postoperative PICU patients; 42 days–23 yrs of age	145	Trend toward an increased incidence of hyponatremia in patients receiving hypotonic IV fluids
Rey et al ¹⁴	PICU patients; 20 months–11 yrs of age	125	Hypotonic IV fluids increased the incidence of hyponatremia in critically ill children
Montañana et al ¹⁵	PICU patients; 29 days–18 yrs of age	122	Hypotonic IV fluids increases the risk of hyponatremia at 24 hr following infusion

IV, intravenous; Na⁺, serum sodium; NS, normal saline; PICU, pediatric intensive care unit

and that using hypotonic saline places children having surgical procedures at risk for cerebral edema. A limitation of this study was the lack of a control group for patients receiving isotonic IV fluids.

Kannan et al⁸ studied the incidence of hyponatremia in 167 hospitalized children by randomizing them to three IV fluids groups: Group A received 5% dextrose (D) and NS at a maintenance rate; Group B received 5% D and 0.18% NaCl at

a maintenance rate; and Group C received 5% D and 0.18% NaCl at 2/3 maintenance rate.⁸ Hyponatremia (Na⁺ <130 mEq/L) occurred in 1 patient (1.72%) in Group A, 8 patients (14.3%) in Group B, and 2 patients (3.8%) in Group C (p=0.028). Hypernatremia (Na >150 mEq/L) occurred in 2 patients in Group A, 2 patients in Group B, and 4 patients in Group C (p=0.59). One patient in Group C developed hyponatremic encephalopathy (p=0.31). Group A patients were eight

times less likely to develop hyponatremia than Group B patients ($p=0.014$). Patients in group C were four times less likely to develop hyponatremia than those in Group B ($p=0.056$). The authors concluded that administration of NS at the maintenance rate helps reduce the incidence of hospital-acquired hyponatremia.

Isotonic Versus Hypotonic IV Fluids Rate versus tonicity

Excessive water intake has been identified as a cause of hyponatremia, so in addition to fluid tonicity, the rate of administration is also important in determining the risk of hyponatremia. We identified two studies in which researchers investigated whether fluid rate or fluid type was associated with acute hyponatremia. The first study, by Yung and Keeley,⁹ evaluated the effects of fluid rate and fluid type on plasma Na concentration in children admitted to the pediatric intensive care unit (PICU). This double-blind, randomized controlled trial included 50 children who received either NS (0.9% NaCl) or D plus saline (4% D and 0.18% NaCl) at either full maintenance rate or 2/3 maintenance rate. Thirty-seven of the 50 patients were postoperative patients. D-saline produced a greater fall in Na⁺ concentration than NS (95% CI, 0.8-5.1). Full maintenance rate IV fluids produced a greater fall in serum sodium concentration than the restricted rate IV fluids (95% CI, -0.7 to 3.9). Surgery patients had a greater fall in mean Na⁺ concentrations than medical patients (2.9 mEq/L and 0.6 mEq/L, respectively). Surgery was a significant covariant for change in Na⁺, as was fluid type ($p < 0.001$) but not fluid rate ($p=0.13$). The authors concluded that fluid type had a greater effect on Na⁺ concentration than fluid rate. Limitations of this study included not recording fluids patients received before PICU admission, which could have affected results. Larger, older children in the NS 100% maintenance IV fluids group could have been effected more as they received less fluid and sodium per kilogram because of a nonlinear increase in fluid and sodium in the use of the Holliday-Segar⁴ method.

Neville et al¹⁰ studied the effects of fluid type versus administration rate of IV maintenance fluid on the development of hyponatremia in postoperative children. The authors randomized 124 children to receive either 2.5% D and NS or ½ NS at 100% maintenance rate or 5% D and NS or ½ NS at 50% maintenance rate. Hyponatremia

(Na⁺ <135 mEq/L) 24 hours after surgery occurred in 21% of patients in the NS 100% maintenance rate group, 8% of patients in the NS 50% maintenance rate group, 22% of patients in the ½ NS 100% maintenance rate group, and 28% of patients in the ½ NS 50% maintenance rate group. Hypernatremia (Na⁺ >145 mEq/L) did not occur in any patient. Adverse events recorded were syndrome of inappropriate antidiuretic hormone secretion (SIADH) in 1 patient in the NS 100% maintenance rate group and 1 patient in the ½ NS 100% maintenance rate group. Dehydration also occurred in 7 patients in the NS 50% maintenance rate group and 7 patients in the ½ NS 50% maintenance rate group. Linear regression analysis showed that fluid type not fluid rate determined risk for hyponatremia ($p < 0.04$). Isotonic saline emerged as protective against development of hyponatremia, and fluid restriction to 50% maintenance emerged as potentially deleterious. Because this study was not blinded, physicians' decisions to give boluses for dehydration could have been biased by knowing their patient was on 50% maintenance fluids.

Surgery patients

Postoperative care for pediatric patients can range from a few hours in the postoperative care unit to several days if admitted to the hospital. Short-term use of hypotonic saline in postoperative patients is not likely to be complicated by dysnatremia, but when recovery is extended and patients receive hypotonic saline for prolonged periods of time, they are at greater risk for developing hyponatremia. Postoperative patients have a higher risk of developing hyponatremia secondary to having multiple stimuli for arginine vasopressin production, including volume depletion, nausea and vomiting, narcotic use, and third spacing. Children 16 years and younger are at a higher risk than adults for developing postoperative hyponatremic encephalopathy, because seizures can occur at higher sodium concentrations in this population due to their relatively larger brain to intracranial volume ratio.² Choong et al¹¹ conducted a randomized, controlled trial comparing isotonic (NS) with hypotonic (½NS) parenteral maintenance fluid for 48 hours in postoperative pediatric patients who underwent elective surgery. Children ages 6 months to 14 years were randomized to receive either hypotonic or isotonic saline IV fluids. Fifty-

three patients (40.8%) in the hypotonic saline group and 29 patients (22.7%) in the isotonic saline group developed hyponatremia ($p=0.004$), defined as Na^+ concentrations less than 134 mEq/L. Eight patients (6.2%) in the hypotonic saline group and 1 patient (0.8%) in the isotonic saline group developed severe hyponatremia ($p=0.59$), defined as Na^+ concentrations less than 129 mEq/L. Five patients (3.9%) in the hypotonic group and 4 patients (3.1%) in the isotonic group developed hypernatremia ($p=0.722$), defined as Na^+ concentrations greater than 146 mEq/L. The adverse event rates were not significantly different between the two groups ($p=0.359$). The risk of hyponatremia was greater with hypotonic IV fluids than with isotonic IV fluids. However, the risk of hypernatremia was not significantly different between the two groups. The authors concluded that isotonic IV fluids is a safer empirical choice than hypotonic IV fluids in protecting against acute postoperative hyponatremia in children. Baseline Na^+ concentrations were not obtained in all patients to determine whether patients developed hyponatremia from IV fluids.

Saba et al¹² randomized 37 medical and postoperative patients between the ages of 3 months and 18 years old requiring IV fluids for at least 8 hours, to receive either isotonic (NS + D5%) or hypotonic ($\frac{1}{2}$ NS + D5%) IV fluids. With average infusion times of 12 hours, Na^+ concentrations increased in both groups but were only significantly higher than at baseline in the isotonic group ($p=0.02$). However, there were no differences in Na^+ concentrations between the groups ($p=0.14$). Hyponatremia, defined as Na^+ less than 136 mEq/L, occurred in 1 patient in the hypotonic group and 1 patient in the isotonic group ($p=1$). There were no adverse events recorded in either group. Hypernatremia, defined as Na^+ concentration greater than 145 mEq/L, occurred in 1 patient in the isotonic IV fluids group. The authors concluded that hypotonic IV fluids administration during the first twelve hours in children did not result in a drop of serum sodium. A limitation to this study includes focusing only on Na^+ concentrations for the first 12 hours after surgery, as longer times on IV fluids with less Na^+ have been linked to hyponatremia.

Au et al¹³ performed a retrospective observational study of postoperative patients ages 42 days to 23 years old admitted to the PICU. The authors reviewed the incidence of hyponatremia

in children receiving isotonic (LR or NS) or hypotonic (all other fluid containing less sodium than 130 mEq/L) IV fluids. "Moderate hyponatremia" ($\text{Na}^+ < 130$ mEq/L) developed in 12 patients in the hypotonic group and 1 patient in the isotonic group ($p=0.423$). "Severe hyponatremia" ($\text{Na}^+ < 125$ mmol/L) developed in 3 patients in the hypotonic group ($p=0.881$). No patients in either group displayed signs/symptoms of acute hyponatremia. The authors concluded there was a trend toward increased incidence of hyponatremia in patients receiving hypotonic IV fluids, but this study lacked the power necessary to determine the exact cause of hyponatremia.

Pediatric Critical Care Patients

Fluid management in the pediatric critical care population is especially complex as many patients require multiple continuous infusions and excess fluid volume due to hypovolemic shock or blood pressure instability. The choice of IV fluids and rate are very important in preventing dysnatremia in the pediatric critical care population. Rey et al¹⁴ studied the effects of hypotonic and isotonic IV fluids on the incidence of dysnatremia in critically ill children. One hundred twenty-five patients were randomized to either a hypotonic saline group (sodium 30-50 mEq/L and potassium 20 mEq/L) or an isotonic saline group (sodium 136 mEq/L and potassium 20 mEq/L). Na^+ levels at 12 hours after admission were 133.7 ± 2.7 mEq/L in the hypotonic group and 136.8 ± 3.5 mEq/L in the isotonic group ($p=0.001$). Na^+ levels 24 hours after admission were 134.2 ± 2.4 mEq/L in the hypotonic group and 136.6 ± 3.1 mEq/L in the isotonic group ($p=0.01$). No differences were found in the incidence of dysnatremia when surgical and nonsurgical patients were compared ($p=0.297$) or in patients who were on mechanical ventilation and those who were not ventilated ($p=0.172$). The authors concluded that hypotonic IV fluids increased the incidence of hyponatremia by 5.8-fold.

Montañana et al¹⁵ randomized 122 patients admitted to the pediatric intensive care unit (PICU) to receive either isotonic ($\text{NaCl} = 140$ mEq/L) or hypotonic ($\text{NaCl} < 100$ mEq/L) IV fluids. The primary endpoint was the percentage of patients who were hyponatremic at 6 and 24 hours after fluid therapy. Hyponatremia ($\text{Na}^+ < 135$ mEq/L) occurred at 6 hours in 20 patients (31.7%) receiving hypotonic saline solution and

in 15 patients (25.4%) receiving isotonic saline solution ($p=0.53$), and at 24 hours in 13 patients (20.6%) receiving hypotonic saline solution and 3 patients (5.1%) receiving isotonic saline solution ($p=0.02$). Severe hyponatremia ($\text{Na}^+ < 125$ mEq/L) occurred in 4 patients (6.3%) in the hypotonic saline group and no patients in the isotonic saline solution at 6 hours ($p=0.12$). Neither group had any patients with severe hyponatremia at 24 hours. Hypernatremia ($\text{Na}^+ > 145$ mEq/L) occurred in 4 patients (6.3%) in the hypotonic saline group and 2 patients (3.3%) in the isotonic saline group at 6 hours ($p=0.68$), in 1 patient (1.6%) in the hypotonic saline group, and in 1 patient (1.7%) in the isotonic saline group at 24 hours ($p=1$). The authors concluded that isotonic IV fluids prevents iatrogenic hyponatremia in PICU patients.

CONCLUSIONS

Hyponatremia is a serious adverse event that can be prevented with appropriate IV fluids choice and careful monitoring. Because hospitalized children are at an increase risk for hyponatremia secondary to nonosmotic stimulus that can stimulate the release of ADH, isotonic IV fluids seems to be a safer empirical choice. The studies discussed demonstrate that the use of isotonic IV fluids can reduce the risk of hospital-acquired hyponatremia. There is evidence to support that hypotonic saline solutions can cause acute hyponatremia, which can lead to serious adverse effects and even death, especially in postoperative patients. Like all drugs, there is no ideal IV fluids for all children, so response to IV fluids therapy should be monitored closely. When hypotonic saline is used health care providers should be educated on the signs and symptoms associated with acute hyponatremia. More studies should be done to determine if hyponatremia occurs more in older populations than in younger patients, since they receive less fluid and sodium per kilogram.

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ABBREVIATIONS ADH, antidiuretic hormone; D, dextrose; ED, emergency department; ISMP, Institute for Safe Medi-

cation Practice; IV, intravenous; LR, lactated Ringer; Na^+ , serum sodium; NaCl, sodium chloride; NS, normal saline; PICU, pediatric intensive care unit; SIADH, syndrome of inappropriate antidiuretic hormone secretion

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