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 **Impact of perioperative hyponatremia in children: A narrative review**

Andersen C *et al.* Perioperative hyponatremia in children

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**Abstract**

For more than 50 years, hypotonic fluids (crystalloids) have been the standard for maintenance fluid used in children. In the last decade, several studies have evaluated the risk of hyponatremia associated with the use of hypotonic versus isotonic fluids, which has lead to an intense debate. Children undergoing surgery have several stimuli for release of antidiuretic hormone, which controls renal water handling, including pain, nausea, vomiting, narcotic use and blood loss. The body’s primary defense against the development of hyponatremia is the ability of the kidneys to excrete free water and dilute urine. Increased levels of antidiuretic hormone can result in hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. This manifests as central nervous system symptoms such as lethargy, irritability and seizures. The risk for symptomatic hyponatremia is higher in children than in adults. It represents an emergency condition, and early diagnosis, prompt treatment and close monitoring are essential to reduce morbidity and mortality. The widespread use of hypotonic fluids in children undergoing surgery is a matter of concern and more focus on this topic is urgently needed. In this paper, we review the literature and describe the impact of perioperative hyponatremia in children.

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**Key words:** Children; Fluid; Hyponatremia; Pediatric; Perioperative

**Core tip:** Hospital-acquired hyponatremia is common, particularly among children undergoing surgery. These children tend to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and they have a poorer prognosis. As the risk is increased by the use of hypotonic fluids, intraoperative fluids for children should be isotonic. Symptomatic hyponatremia should be corrected with 3% sodium chloride and close monitoring of the patient and serum sodium level is mandatory to prevent brain herniation and neurologic damage from cerebral ischemia.

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**INTRODUCTION**

The overall goal of perioperative fluid management is to ensure adequate perfusion of tissue by administering maintenance fluids including electrolytes and glucose to replace preoperative fluid deficits and ongoing losses. Preoperative fluid status in children is affected by various factors, and a deficit is often due to prolonged fasting, dehydration (from diarrhea, vomiting and fever), bleeding and increased levels of stress. Inadequate fluid management may cause reduced cardiac output and oxygen delivery to damaged tissue, which is associated with an increased rate of postoperative complications[1]. On the other hand, overhydration can have equally severe consequences, such as acidosis, coagulation deficits and peripheral and pulmonary edema[2-5].

Children undergoing surgery are at a higher risk for developing hyponatremia, defined as a plasma sodium level < 136 mmol/L, which causes cells to draw in excess water and swell. Accumulating evidence indicates that among those with a serum sodium < 125 mmol/L, more than 50% develop hyponatremic encephalopathy and are at a risk for seizure, respiratory failure and ultimately death[6-9]. Thus, correct perioperative fluid management is essential to avoid perioperative hyponatremia. This review discusses the recent evidence concerning this important and often neglected clinical condition in children.

**MAINTENANCE FLUID IN CHILDREN**

The calculation of maintenance fluid in children is based on Holliday and Segar’s recommendations from 1957[10]. They described the physiologic deficits that result from fluid lost from the skin, respiratory tract, and urine, equivalent to approximately 100 mL/100 kcal metabolized per day. Their calculations have since evolved into the widely used “4-2-1 rule” (Table 1)[11,12]. However, this formula provides only for water maintenance, and does not consider correction of deficits or replacement of continuous, abnormal water loss. In 1975, Furman *et al*[13] suggested calculating the preoperative deficits by multiplying the hourly rate by the number of hours the patient was *nil per os*. Furthermore, they proposed replacing half of this deficit during the first hour of surgery, followed by administration of the other half over the next two hours. This method was simplified in 1986 by Berry[14] who proposed delivering a bolus of a 0.9% normal saline solution to otherwise healthy children over the first hour of surgery. Berry concluded that children three years of age and younger should receive 25 mL/kg, whereas children four years and older should receive 15 mL/kg. These methods were based on the assumption that the patients had been under *nil per os* for at least 6–8 h, thought recent liberalization of fasting requirements may have decreased preoperative water loss[15-17].

**PERIOPERATIVE HYPONATREMIA IN CHILDREN**

Hyponatremia is the most common electrolyte abnormality found in hospitalized children[18,19]. The body’s primary mechanism to prevent hyponatremia is the generation of dilute urine and excretion of free water by the kidneys. Renal water handling is generally controlled via antidiuretic hormone[20], the release of which is stimulated by pain, nausea, vomiting, narcotic use and blood loss, among others (Table 2), which are experienced by many children undergoing surgery[21,22]. Antidiuretic hormone can promote hyponatremia by increasing the permeability of collecting duct cells in the kidney, leading to the retention of free water. Subsequent influx of water into the brain via glial cell swelling can lead to cerebral edema, brain stem herniation and death[23-33].

Pediatric patients are more prone to symptomatic hyponatremia[34-38], which is mainly manifested as central nervous system symptoms, including lethargy, irritability, muscle weakness, seizures and coma or even death, in the most severe cases[39-42]. Furthermore, children undergoing surgery are also more likely to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults, with an estimated mortality of 8%[6]. Symptoms of hyponatremic encephalopathy are often unspecific and may appear as headache, nausea, vomiting and fatigue, which can easily be mistaken for normal symptoms after surgery and general anesthesia[24,43-47], but can rapidly progress to seizures, respiratory arrest and ultimately death or a permanent vegetative state as a complication of severe cerebral edema[48]. The associated poorer prognosis is probably due to a combination of physical and physiologic differences between adults and children[49,50]. Children have a higher brain:skull size ratio, as their brains reach adult size by six years of age, which is ten years before their skulls attain their final dimensions. One should keep in mind that in older adults, there is a progressive loss of brain volume whilst the volume inside the skull remains constant.

Critically ill children, and those in need of postoperative admission to intensive care units, are particularly at an increased risk for hyponatremia[51-57]. Hyponatremia in these children can be caused by normo- or hypervolemic conditions caused by heart failure, such as iatrogenic-induced hyponatremia (secondary to excessive water and/or salt insufficiency), renal insufficiency or a syndrome of inappropriate antidiuretic hormone secretion[58], or by hypovolemia from extra-renal volume loss (gastric, diarrhea, burn wounds, interstitial leakage), renal loss (polyuria after acute kidney failure, adrenocortical insufficiency) or excessive use of diuretics. Children with neurologic diseases, younger children with intracranial neoplasms, and those with hydrocephalus are also more prone to hyponatremia, which can be more complicated[59-67]. In a recent study, hyponatremic children with intracranial neoplasms had a five-fold increased risk of moderate or severe disability based on their Pediatric Cerebral Performance Category score at discharge, with hyponatremia independently associated with worse neurologic outcome despite adjustment for age and tumor factors[68]. They same group also found an increased risk of postoperative hyponatremia after neurosurgery among children that was independent of the preoperative degree of hyponatremia[69]. However, there was a greater variation in serum sodium levels among the children with the most severe preoperative hyponatremia. Additionally, obstructive hydrocephalus and < 3.5 years of age were identified as significant independent risk factors for severe hyponatremia among those affected.

The risk for hospital-acquired hyponatremia and hyponatremic encephalopathy have been related to the use of hypotonic intravenous solutions[6,70-77]. Wang *et al*[78]found a significantly higher risk for hyponatremia and severe hyponatremia among pediatric patients administered hypotonic solutions compared with isotonic fluids in a systematic review of ten randomized clinical trials involving 855 subjects. Hyponatremia is also a concern in neonates, as intravenous hypotonic and free water intake of more than 6.5 mL/kg per hour during surgery reduces the number of postoperative plasma sodium measurements > 4 mmol/L[79,80]. Additionally, there was an adverse association between large (8–13 mmol/L) and very large (> 13 mmol/L) changes in serum sodium levels in the first few weeks of life and the risk of impaired functional outcomes at two years of age, with neuromotor impairments in particular.

**CORRECTION OF HYPONATREMIA**

To prevent brain herniation and neurologic damage from cerebral ischemia, cases of symptomatic hyponatremia require urgent correction of sodium levels to 4–6 mmol/L with 3% sodium chloride[48,81-86]. The rate of correction does not need to be restricted in patients with true acute hyponatremia, and modulation of excessive corrections is not indicated[87]. However, limits for correction are warranted if there is any uncertainty as to whether the hyponatremia is chronic or acute. It should be noted that correction of hypokalemia will also contribute to an increase in the serum sodium concentration. In the absence of severe or moderately severe symptoms, there is often sufficient time for diagnostic assessment and cause-specific treatment. Although children with severe hyponatremia need urgent, frequent and prolonged monitoring because of the risk of repeated sodium changes[69], correction with hypertonic saline is not indicated in asymptomatic cases[88,89].

**CONCLUSION**

As the use of hypotonic fluids is related to a higher risk of hyponatremia compared with isotonic fluids[90-93], it is difficult to justify their widespread use as a standard maintenance fluid in children during surgery. An ideal intraoperative fluid should have a tonicity and sodium concentration close to the physiologic range[94]. To avoid lipolysis, hypoglycemia, or hyperglycemia, 1.0%–2.5% glucose (rather than 5%) should be used and should also include metabolic anions (*i.e.* acetate, lactate or malate) as bicarbonate precursors to prevent hyperchloremic acidosis. Most children need 2–3 mEq/kg per 24 h of sodium chloride, and the target serum sodium is between 135–140 mmol/L.

Monitoring of serum sodium levels in patients maintained by fluid infusion is critical, and certainly in children undergoing surgery as they are more vulnerable to hyponatremia than adults. Indeed, close monitoring is mandatory in symptomatic cases of hyponatremia, as they can rapidly progress to hyponatremic encephalopathy[95-100]. This complex problem remains an ongoing clinical challenge and deserves more attention by clinicians, not only in an academic context, but in clinical settings where there is ample evidence to support fluid therapy strategies that can reduce the risk of serious consequences for children. Additionally, the medical industry and researchers should increase their efforts to develop more appropriate and balanced intravenous solutions for children of various ages and conditions, due to the diverse availability of solutions across geographical regions (Table 3).

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# Table 1 The 4-2-1 formula for maintenance fluids in children[10,11]

|  |  |  |
| --- | --- | --- |
| **Weight** | **Daily fluid requirements** | **Hourly fluid requirements** |
| 3–10 kg | 100 mL/kg | 4 mL/kg per hour |
| 11–20 kg | 1000 mL + 50 mL for every kilogram > 11 | 40 mL/h + 2 mL/h for every kilogram > 11 |
| >20 kg | 1500 mL+ 20 mL for every kilogram >20 | 60 mL/h + 1 mL/h for every kilogram > 20 |

**Table 2** **Stimuli associated with increased antidiuretic hormone production (adapted from Bailey[15])**

|  |
| --- |
| **Hemodynamic** |
| Hypotension |  |
| Hypovolemia | Blood loss, diarrhea, diuretics, vomiting, renal salt wasting, hypoaldosteronism, burns, polyuria |
| Hypervolemia | Nephrotic syndrome, cirrhosis, heart failure, hypoalbuminemia, iatrogenic-induced hyponatremia, excessive water intake |
| **Nonhemodynamic** |
| Central nervous system disturbances | Meningitis, encephalitis, brain abscess, head injury, hypoxic brain injury, stroke |
| Pulmonary diseases | Asthma, pneumonia, chronic obstructive pulmonary disease, tuberculosis, empyema, bronchiolitis, acute respiratory failure |
| Cancer | Lung cancer (especially small-cell lung cancer), brain tumor, leukemia, lymphoma, pancreatic cancer, prostate cancer, ovarian cancer, neuroendocrine tumor, squamous cell carcinoma  |
| Medications | Selective serotonin reuptake inhibitors, morphine, carbamazepine, cyclophosphamide, vincristine, desmopressin |
| Other | Pain, stress, nausea, emesis, postoperative state, cortisol deficiency |

**Table 3 Most commonly available crystalloid and human albumin solutions in Europe**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Fluid** | **Na2+ (mmol/L)** | **K+****(mmol/L)** | **Cl-****(mmol/L)** | **Lactate (mmol/L)** | **Acetate****(mmol/L)** | **Glucose monohydrate (g/L)** | **Osmolarity****(mOsm/L)** | **Tonicity****(to plasma)** |
| Isotonic NaCl2 | 154 | 0 | 154 | 0 | 0 | 0 | 308 (iso-osmolar) | Isotonic |
| Ringer’s lactate | 130 | 4 | 109 | 28 | 0 | 0 | 270 (iso-osmolar) | Isotonic |
| Ringer’s acetate | 130 | 4 | 110 | 0 | 30 | 0 | 270 (iso-osmolar) | Isotonic |
| Darrow-glucose “SAD” | 31 | 9 | 26 | 14 | 0 | 55 | 360 (hyperosmolar) | Hypotonic |
| Human albumin 5% | 130 – 160 | <3 | 0 | 0 | 0 | 0 | 330 (hyperosmolar) | Isotonic |
| Human albumin 20% | 100 – 160 | <3 | 0 | 0 | 0 | 0 | 300 (hyperosmolar) | Hypertonic |
| Glucosalin 2:1(Glucose 3.3%/NaCl2 0.3%) | 51 | 0 | 51 | 0 | 0 | 33 | 287 (iso-osmolar) | Hypotonic |
| Glucose 2.5%/NaCl2 0.45% | 77 | 0 | 77 | 0 | 0 | 25 | 293 (iso-osmolar) | Hypotonic |
| Glucose 4%/NaCl2 0.18% | 31 | 0 | 31 | 0 | 0 | 40 | 284 (iso-osmolar) | Hypotonic |
| Glucose 5%/NaCl2 0.45% | 77 | 0 | 77 | 0 | 0 | 50 | 432 (hyperosmolar) | Hypotonic |
| Glucose 4.6%/NaCl2 0.9% | 154 | 0 | 154 | 0 | 0 | 46 | 561 (hyperosmolar) | Isotonic |
| Glucose 9.1%/NaCl2 0.9% | 154 | 0 | 154 | 0 | 0 | 91 | 813 (hyperosmolar) | Isotonic |
| Glucolyte(Glucose 5%/NaCl2 0.3%/KCl 0.15%) | 51 | 20 | 71 | 0 | 0 | 50 | 420 (hyperosmolar) | Hypotonic |