Hospital-acquired hyponatremia in postoperative pediatric patients: Prospective observational study*

Pablo G. Eulmesekian, MD; Augusto Pérez, MD; Pablo G. Minces, MD; Desmond Bohn, MB, FRCPC

**Objective:** To establish the incidence and factors associated with hospital-acquired hyponatremia in pediatric surgical patients who received hypotonic saline (sodium 40 mmol/L plus potassium 20 mmol/L) at the rate suggested by the Holliday and Segar’s formula for calculations of maintenance fluids.

**Design:** Prospective, observational, cohort study.

**Setting:** Pediatric intensive care unit.

**Patients:** Eighty-one postoperative patients.

**Interventions:** None.

**Measurements and Main Results:** Incidence and factors associated with hyponatremia (sodium < 135 mmol/L). Univariate analysis was conducted post surgery at 12 hrs and at 24 hrs. Mean values were compared with independent t test samples. Receiver operating characteristics curve analysis was performed in variables with a p < .05, and relative risks were calculated. Eighty-one patients were included in the study. The incidence of hyponatremia at 12 hrs was 17 (21%) of 81 (95% confidence interval, 3.7–38.3); at 24 hrs, it was 15 (31%) of 48 (95% confidence interval, 11.4–50.6). Univariate analysis at 12 hrs showed that hyponatremic patients had a higher sodium loss (0.62 mmol/kg/hr vs. 0.34 mmol/kg/hr, p = .0001), a more negative sodium balance (0.39 mmol/kg/hr vs. 0.13 mmol/kg/hr, p < .0001), and a higher diuresis (3.08 mL/kg/hr vs. 2.2 mL/kg/hr, p = .0026); relative risks were 11.55 (95% confidence interval, 2.99 – 44.63; p = .0004) for a sodium loss > 0.5 mmol/kg/hr; 10 (95% confidence interval, 2.55 – 39.15; p = .0009) for a negative sodium balance > 0.3 mmol/kg/hr; and 4.25 (95% confidence interval, 1.99 – 9.08; p = .0002) for a diuresis > 3.4 mL/kg/hr. At 24 hrs, hyponatremic patients were in more positive fluid balance (0.65 mL/kg/hr vs. 0.10 mL/kg/hr, p = .0396); relative risk was 3.25 (95% confidence interval, 1.2–8.77; p = .0201), for a positive fluid balance > 0.2 mL/kg/hr.

**Conclusions:** The incidence of hyponatremia in this population was high and progressive over time. Negative sodium balance in the first 12 postoperative hours and then a positive fluid balance could be associated with the development of postoperative hyponatremia. (Pediatr Crit Care Med 2010; 11:479 – 483)

**KEY WORDS:** hyponatremia; children; postoperative; hospital-acquired hyponatremia; hypotonic fluids

*See also p. 528.

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A hypotonic saline in pediatric practice was prescribed to replace insensible losses in patients unable to take oral fluids. The formula used in the calculation that established the use of hypotonic solutions administered as maintenance fluids in the widespread perioperative use of hypotonic saline in pediatric practice was developed by Malcolm A. Holliday and William E. Segar and published 50 yrs ago (1). The validity of the assumptions used in calculation of the water and electrolyte requirements for normal homeostasis have recently been called into question because the amount of electrolyte free water administered can result in the development of acute hyponatremia (2, 3).

There are >50 case reports or case series published in the medical literature of death or neurologic injury from cerebral edema associated with acute hyponatremia in children. A significant number of these have occurred in the postoperative period where the combination of the administration of electrolyte free water and nonphysiologic secretion of antidiuretic hormone puts children at significant risk of this complication (4–12). Nevertheless, comprehensive evaluations of the incidence and mechanisms of postoperative acquired hyponatremia in a pediatric intensive care setting are scarce. Dearlove et al (13), Armon et al (14), and Snaith et al (15) focused on general pediatric patients and did not differentiate between preexisting and hospital-acquired hyponatremia. Halberthal et al (8) and Hoorn et al (16) focused on hospital-acquired hyponatremia but included both medical and postoperative patients. Au and colleagues (17) studied postoperative hyponatremia in pediatric intensive care patients but they only considered as hyponatremia a sodium concentration of <130 mmol/L. However, this threshold to define postoperative acquired hyponatremia could potentially compromise patient safety.

The objective of this prospective observational study was to establish the incidence and factors associated with hospital-acquired hyponatremia in a cohort of pediatric patients admitted to intensive care for postoperative management and who were prescribed hypotonic saline at rates based on the Holliday and Segar formula for calculating maintenance fluids (1).

METHODS

Population and Inclusion Criteria

Data were collected prospectively on consecutive postoperative children admitted to the pediatric intensive care unit (PICU) between June 1, 2005 to June 1, 2006, if they met the following inclusion criteria: a) baseline plasma sodium (PNa) between 136 and 144 mmol/L; b) postoperative order for maintenance fluids in the form of intravenous (IV) hypotonic saline (Na 40 mmol/L + K 20 mmol/L); c) IV fluid to be administered for at least 12 hrs at a rate ≥70% of the amount calculated using Holliday and Segar’s formula for requirements of maintenance fluids (1).

Exclusion Criteria

Patients were excluded from the study for the following reasons: a) lack of informed consent; b) order prescribed for maintenance fluids contained Na >40 mmol/L; c) positive balance of isotonic fluid >20% of maintenance (isotonic saline administered – drain losses); d) development of hyperglycemia (glucose >11 mmol/L) (18); e) administration of IV mannitol; f) sustained body temperature of >38°C.

End of the Study

The primary end point was development of hyponatremia. Patients ended the study if a) they developed hyponatremia (PNa <136 mmol/L) (19); b) the order for IV administration rate was decreased to <70%; c) the Na concentration of the maintenance fluids was increased to >40 mmol/L; d) enteral fluids were started; or e) 48 hrs had elapsed from the commencement of the study. As this was an observational study, patients who developed hyponatremia were managed by their attending physician.

Data Collection and Calculations

The following data were collected: a) patient demographics; b) the Pediatric Index of Mortality (PIM2) (20); c) duration of IV hypotonic fluid administration; d) the PNa and plasma potassium at PICU admission and every 12 hrs; e) urine sodium and urine potassium in patients with a urinary catheter; and f) fluid intake and output.

Table 1. Patient demographics (n = 81 patients)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ± SEM)</td>
<td>9.78 ± 0.69</td>
<td></td>
</tr>
<tr>
<td>Mortality Predicted by PIM2 in % (mean ± SEM)</td>
<td>1.12 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>LOS, days (mean ± SEM)</td>
<td>1.81 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>Weight, kg (mean ± SEM)</td>
<td>34.6 ± 2.4</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>F 45 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Ventilated, n (%)</td>
<td>M 36 (44.4)</td>
<td></td>
</tr>
<tr>
<td>General surgery, n (%)</td>
<td>13 (16)</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery, n (%)</td>
<td>34 (42)</td>
<td></td>
</tr>
<tr>
<td>Thoracic surgery, n (%)</td>
<td>31 (38.3)</td>
<td></td>
</tr>
<tr>
<td>Plastic Surgery, n (%)</td>
<td>13 (16)</td>
<td></td>
</tr>
<tr>
<td>0–10 kg</td>
<td>3 (3.7)</td>
<td></td>
</tr>
<tr>
<td>10–20 kg</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>20–30 kg</td>
<td>11 (14)</td>
<td></td>
</tr>
<tr>
<td>30–40 kg</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td>40–50 kg</td>
<td>12 (15)</td>
<td></td>
</tr>
<tr>
<td>50–60 kg</td>
<td>9 (11)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 kg</td>
<td>14 (17)</td>
<td></td>
</tr>
<tr>
<td>PIM2, Pediatric Index of Mortality 2; LOS, length of stay.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PNa and potassium were measured in our central laboratory by indirect potentiometry with two ion selective electrodes, using a Synchro-chron LX20 machine (Beckman Coulter Inc., Brea, CA). Blood samples were taken in 1-mL heparinized syringe (heparin solution with a sodium concentration of 135 mmol/L). Intrasample variability was measured in the same sample five times in five patients. Coefficient of variation (SD/mean) was 1%.

Urine sodium and potassium were also measured in our central laboratory by the same technology. Only those patients who came back from the operating room with a urinary catheter in place had their urine samples sent for electrolyte measurements. Urine samples were collected for periods of 6 hrs, and all 6-hr samples were sent to the laboratory. First, 12-hr urine electrolytes were averaged from the first two samples, then 12-hr to 24-hr urine electrolytes were averaged from the following two samples.

To differentiate the potential causes of hyponatremia into those due to the administration of fluids with a significant component of electrolyte free water vs. the loss of Na, we performed fluid balance in all patients and Na balance in those who had urine electrolytes measured (3, 21, 22).

### Statistical Analysis

The D’Agostino-Pearson test was used to confirm or reject normal distribution of variables. Mean and SEM values were used. Univariate analysis was conducted postoperatively at 12 hrs and 24 hrs. Means of variables in hyponatremic and isonatremic patients were compared by independent t test samples. Receiver operating characteristics curve analysis was performed in variables with a p < .05 to obtain cutoff values. Relative risks were calculated. MedCalc 9.0 software was used for statistical analysis.

Study protocol was approved by our Institutional Review Board, and informed consent was obtained from the parents or legal guardians of all children.

### RESULTS

Between June 1, 2005 and June 1, 2006, there were 283 postoperative patients admitted to the unit, and 99 fulfilled the inclusion criteria (Fig. 1). Eighteen patients were excluded from the analysis; thus, the total number of patients included in the study was 81. Patient demographics are shown in Table 1. The timeline of the study is shown in Figure 2. Eighty-one patients completed 12 hrs of the study, and 48 patients received 24 hrs of IV fluids. Thirty-five patients who completed 12 hrs of the study and 21 of 48 patients who completed 24 hrs had urine samples available for measurement of electrolytes and calculation of Na balance.

The incidence of hospital-acquired hyponatremia at 12 hrs was 17 (21%) of 81 (95% confidence interval [CI], 3.7–38.3); at 24 hrs, it was 15 (31%) of 48 (95% CI, 11.4–50.6). No patient, 0 (0%) of 81 (95% CI, 0–4.53), developed PNa<130 mmol/L, neurologic adverse events (seizures or changes in sensorium), or died. There was no significant difference be-

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### Table 2. Univariate analysis of variables studied at 12 hrs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Isonatremic</th>
<th>Hyponatremic</th>
<th>Diff</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>64</td>
<td>9.75</td>
<td>0.76</td>
<td>17</td>
<td>9.89</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>64</td>
<td>35.64</td>
<td>2.77</td>
<td>17</td>
<td>30.71</td>
</tr>
<tr>
<td>PNa 0 hs (mmol/L)</td>
<td>64</td>
<td>139.59</td>
<td>0.27</td>
<td>17</td>
<td>138.65</td>
</tr>
<tr>
<td>PNa 12 hs (mmol/L)</td>
<td>64</td>
<td>138.03</td>
<td>0.24</td>
<td>17</td>
<td>133.35</td>
</tr>
<tr>
<td>Hypot Fl In (mL/kg/hr)</td>
<td>64</td>
<td>2.61</td>
<td>0.15</td>
<td>17</td>
<td>3.17</td>
</tr>
<tr>
<td>Urine (mL/kg/hr)</td>
<td>64</td>
<td>2.20</td>
<td>0.11</td>
<td>17</td>
<td>3.08</td>
</tr>
<tr>
<td>Fl Bal (mL/kg/hr)</td>
<td>64</td>
<td>0.16</td>
<td>0.12</td>
<td>17</td>
<td>-0.31</td>
</tr>
<tr>
<td>Na In (mmol/kg/hr)</td>
<td>64</td>
<td>0.22</td>
<td>0.01</td>
<td>17</td>
<td>0.25</td>
</tr>
<tr>
<td>Na Out (mmol/kg/hr)</td>
<td>25</td>
<td>0.34</td>
<td>0.02</td>
<td>10</td>
<td>0.62</td>
</tr>
<tr>
<td>Na Bal (mmol/kg/hr)</td>
<td>25</td>
<td>-0.13</td>
<td>0.02</td>
<td>10</td>
<td>-0.39</td>
</tr>
<tr>
<td>UNa + UK (mmol/L)</td>
<td>25</td>
<td>178.16</td>
<td>13.66</td>
<td>10</td>
<td>194.30</td>
</tr>
</tbody>
</table>

CI, confidence interval; PNa, plasma sodium; Hypot Fl In, hypotonic fluids in; Fl Bal, fluids balance; Na Bal, sodium balance; UNa + UK, urinary sodium plus potassium.

Considering insensible losses that were calculated in 14 mL/kg/day (16).
The incidence of hyponatremia reported here is higher than the one recently described by Au et al (17). They studied retrospectively a cohort of postoperative critically ill children receiving hypertonic solutions and found that 12.9% had hyponatremia, which they defined as Na < 130 mmol/L. The threshold we applied (Na ≥ 135 mmol/L) (19) was more conservative and could reasonably explain the higher occurrence rate found. The kind of design used, i.e., prospective and observational, precluded opting for a different value because patient safety could have been compromised. The importance of recognizing mild hyponatremia as a frequent event is to alert physicians and provide the adequate time for appropriate interventions to avoid additional decreases in natremia and potential complications.

The variables associated with hyponatremia varied at 12 and 24 postoperative hrs. Patients who became hyponatremic at 12 hrs had a higher Na loss, a more negative Na balance, and a higher diuresis than patients who remained isonatremic (Table 2). These findings may be similar to those characteristic of the phenomenon of “desalination,” reported by Steele and colleagues (22); they found a fall in PNa in adults after elective surgical procedures when near isotonic fluid (Ringer’s lactate) was used. They also observed that a good urine output may be a potential risk for developing postoperative hyponatremia. We hypothesize a similar situation for this population: Overexpansion of the extracellular fluid compartment due to fluid administration during surgery combined with the nonphysiologic stimulation of antidiuretic hormone results in the production of hypertonic urine and postoperative hyponatremia.

Patients who became hyponatremic at 24 hrs after surgery had a higher input of Na and a more positive fluid balance (Table 3). The higher Na input is likely not associated with hyponatremia and could be related to the higher input of hypertonic fluids that hyponatremic patients received (2.97 mL/kg/hr vs. 2.56 mL/kg/hr, p = .2872). Therefore, positive fluid balance at this time point remained the only variable associated with hyponatremia. This finding also indicates that negative Na balance occurs during the first postoperative hours.

The current study was done in children having major surgical procedures requiring admission to the PICU for postoperative observation and management. Thirty-eight percent had orthopedic surgery. This population is a group particularly at risk. Burrows and colleagues (23), in a controlled trial of postoperative fluids, compared hypertonic saline and Ringer’s lactate. Both groups had a fall in PNa, which was more significant in those receiving hypertonic fluid. Brazel and McPhee (24) did a similar study in patients with scoliosis and followed their fluid and electrolyte balance for 48 hrs. They found that patients receiving hypertonic fluids had a fall in PNa to a mean of 130 mmol/L at 24 hrs after surgery, with the lowest value being 119 mmol/L. In eight of 12 patients, the lowest PNa value was seen at the 24-hr to 48-hr mark. Despite the marked hyponatremia, patients were monitored closely for the development of symptoms of hypothemia (25).
tremia, patients failed to produce dilute urine, clear evidence that there was non-
physiologic secretion of antidiuretic hor-
mones. Patients with scoliosis may also be
particularly at risk because the blood loss
is usually considerable and, therefore, the
amount of intraoperative fluids adminis-
tered may lead to volume overexpansion
and a setup for desalination.

Our study provides further evidence
that the use of hypotonic saline, as sug-
gested by Holliday and Segar's formula
for maintenance fluids in postoperative
management, is associated to a high oc-
currence rate of acute hyponatremia.
Despite an increasing number of publica-
tions suggesting that the use of
hypotonic saline places children at risk
(2, 25–27), this type of fluid continues to
be prescribed. In a recent survey of the
prescribing habits of anesthesiologists
who anesthetize children in the United
Kingdom, 66% said they would use hypo-
tonic saline in the perioperative period,
and 87% said they would prescribe it
for postoperative maintenance fluid (28).
Perhaps of even more concern is that
a survey of anesthesiology and surgery
trainees showed that only approximately
one third can correctly identify the Na
concentration of 0.9 NaCl (29, 30).

This study does have some limitations.
These include the inherent-to-the-design
lack of a control group who received iso-
tonic saline; data not available on the
amount of intraoperative fluids received;
calculations of Na balance based on 43%
of the population; and finally, data not
available on Na levels beyond 24 post-
operative hours.

In conclusion, the incidence of hospi-
tal-acquired hyponatremia in this popu-
lation of postoperative patients admitted
to the PICU and who received mainte-
nance fluids in the form of hypotonic
saline in accordance with the standard
recommendations, was high and progres-
sive over time. Negative Na balance in the
first 12 hrs and a positive fluid balance
could be major contributors to the de-
velopment of hyponatremia in postoperative
patients. This raises the question as to
whether the use of isotonic saline in
lesser amounts than currently recom-
ended for maintenance requirements
would be a better choice. This article,
thus, assists the clinician in an under-
standing of the frequency of severe hypo-
natremia and how to best detect it.

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