Hypotonic Versus Isotonic Maintenance Fluids After Surgery for Children: A Randomized Controlled Trial

WHAT’S KNOWN ON THIS SUBJECT: The role of hypotonic parenteral solutions in the pathogenesis of hospital-acquired hyponatremia in children has been much debated for almost 2 decades, but there has been a paucity of prospective trials evaluating the safety of common maintenance solutions for children.

WHAT THIS STUDY ADDS: The results confirm that hypotonic solutions increase the risk of postoperative hyponatremia in children, whereas this risk is significantly reduced with isotonic fluids. The number needed to treat with isotonic maintenance solutions to prevent 1 case of hyponatremia is 6.

abstract

OBJECTIVE: The objective of this randomized controlled trial was to evaluate the risk of hyponatremia following administration of a isotonic (0.9% saline) compared to a hypotonic (0.45% saline) parenteral maintenance solution (PMS) for 48 hours to postoperative pediatric patients.

METHODS: Surgical patients 6 months to 16 years of age with an expected postoperative stay of >24 hours were eligible. Patients with an uncorrected baseline plasma sodium level abnormality, hemodynamic instability, chronic diuretic use, previous enrollment, and those for whom either hypotonic PMS or isotonic PMS was considered contraindicated or necessary, were excluded. A fully blinded randomized controlled trial was performed. The primary outcome was acute hyponatremia. Secondary outcomes included severe hyponatremia, hypernatremia, adverse events attributable to acute plasma sodium level changes, and antidiuretic hormone levels.

RESULTS: A total of 258 patients were enrolled and assigned randomly to receive hypotonic PMS (N = 130) or isotonic PMS (N = 128). Baseline characteristics were similar for the 2 groups. Hypotonic PMS significantly increased the risk of hyponatremia, compared with isotonic PMS (40.8% vs 22.7%; relative risk: 1.82 [95% confidence interval: 1.21–2.74]; P = .004). Admission to the pediatric critical care unit was not an independent risk factor for the development of hyponatremia. Isotonic PMS did not increase the risk of hypernatremia (relative risk: 1.30 [95% confidence interval: 0.30–5.59]; P = .722). Antidiuretic hormone levels and adverse events were not significantly different between the groups.

CONCLUSION: Isotonic PMS is significantly safer than hypotonic PMS in protecting against acute postoperative hyponatremia in children.

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Key Words: hypotonic, isotonic, intravenous fluids, clinical trial

Abbreviations: PMS—parenteral maintenance solution, ADH—antidiuretic hormone, EFW—electrolyte-free water, RR—relative risk, PCCU—pediatric critical care unit, CI—confidence interval

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The emergence of severe neurologic morbidity and deaths resulting from iatrogenic hyponatremia has raised questions regarding the safety of the widely used Holiday-Segar recommendations for parenteral maintenance solutions (PMSs) and has fueled furious debate regarding whether hypotonic or isotonic solutions are more appropriate for hospitalized children.1–4 Hospital-acquired hyponatremia is common, and children undergoing surgery are at particular risk.5–7 Proposed mechanisms for hyponatremia include the following: nonosmotic antidiuretic hormone (ADH) secretion and impaired electrolyte-free water (EFW) clearance,8 cerebral salt wasting,9 a “desalination” phenomenon,10 transloca-tional hyponatremia, and the sick cell syndrome.11 Although it is increasingly being suggested that hypotonic PMS increases the risk of hyponatremia, prospective evidence comparing the safety of hypotonic and isotonic PMSs for children is limited.12 Those in favor of isotonic PMS argue that it supports the most important role of sodium during acute illness by maintaining plasma tonicity, whereas hypotonic PMS results in excess EFW in patients with an already impaired ability to excrete EFW.13 Those who favor hypotonic PMS argue that hyponatremia results from excessive PMS volume (as opposed to PMS type) and there are unacceptable risks with isotonic PMS, such as hyponatremia, interstitial fluid overload, excessive sodium excretion, and hyperchloremic metabolic acidosis.14–16 The primary objective of this fully blinded, randomiz-ed controlled trial was to determine whether isotonic PMS administered at traditional maintenance rates to children in the acute postoperative period decreased the risk of hyponatremia, when compared to hypotonic PMS.

METHODS

Participants
This trial was approved by the institutional ethics board and was conducted at McMaster Children’s Hospital (Hamilton, Ontario, Canada). Informed consent and assent, where appropriate, were obtained before patient enrollment. Euvolemic patients, 6 months to 16 years of age, within 6 hours after elective surgery were eligible if their anticipated need for PMS was >24 hours. The following patients were excluded: patients with uncorrected plasma sodium level abnormalities before the end of surgery, patients with known abnormalities of ADH secretion, patients requiring volume resuscitation and/or vasoactive infusions, recent loop diuretic use, total parenteral nutrition required within 24 hours following surgery; and patients for whom either a hypotonic or isotonic PMS was considered necessary or contraindicated (e.g. because of a risk of cerebral edema, acute burns, or the risk of third space and/or sodium overload in patients with pre-existing congestive cardiac failure, renal failure, liver failure or cirrhosis).

Randomization
Participants were assigned randomly, with equal chances of being assigned to receive isotonic PMS or hypotonic PMS. The computer-generated randomization sequence was prepared by a statistician (in a 1:1 ratio), using block sizes of 6 and stratified according to postoperative admission ward, that is, pediatric critical care unit (PCCU) or general surgical ward. The randomization code was maintained by the research pharmacist and was concealed from all research personnel. All participants, medical and research staff members, investigators, and data safety monitoring committee members were blinded with respect to the group assignments. To ensure prompt access to and administration of the intervention after randomization, the masked study solutions were numbered consecutively and were stored in individual, correspondingly numbered containers in a secure location that was accessible only to research personnel. Research assistants enrolled participants and assigned the intervention from the sequentially numbered study containers. Additional study solutions required during the intervention period were dispensed by the pharmacy.

Trial Intervention
Masked solutions were prepared by the research pharmacist; 0.45% saline was used as the hypotonic PMS and 0.9% saline as the isotonic PMS. Both solutions were administered with 5% dextrose unless otherwise specified. Potassium chloride was added according to the treating physician’s request. Solutions were repackaged individually in identical, sealed, opaque bags, identified only with the study number, additives (e.g. potassium chloride concentration), and the patient’s name (after random assignment). Fluids were administered intravenously according to the anesthetist’s discretion. With the exception of patients with indwelling invasive lines, a saline lock was inserted at the end of surgery specifically for study blood sampling. Because of this study procedure, informed consent was obtained before surgery when possible and full eligibility was confirmed after surgery, before patient assignment. Samples for plasma sodium measurements and urine sodium and potassium measurements were obtained every 12 hours and those for plasma ADH measurements were obtained every 24 hours during the study period. The intervention was administered as soon as possible after random assignment after surgery, for a maximum of 48 hours. The rate and total duration of PMS ad-
ministration, as well as all other aspects of clinical care (eg, replacement fluids, diet, medications, and additional tests), were determined by the treating physician. Patients who required PMS administration beyond 48 hours were changed to solutions of the physician’s choice. Participants were monitored until hospital discharge or a maximum of 48 hours after the intervention was discontinued.

All caregivers were blinded with respect to study-specific investigation results. To ensure patient safety, an independent medical safety officer reviewed all masked plasma sodium level results and referred the treating physician to the clinical pathways for managing acute plasma sodium level derangements if predefined thresholds were met (Appendices 1–3). In the event of persistent electrolyte abnormalities, the treating physician had the option of changing the study solution to an open-label PMS of his or her choice without unblinding the intervention. The reasons for changing to an open-label PMS were recorded. Electrolyte levels were measured through indirect ion-selective electrode testing (Roche Modular Analytics, Laval, Quebec, Canada). Plasma ADH levels were measured by radioimmunoassay, as described previously.

### Outcome Measures

The primary outcome was hyponatremia (plasma sodium level of ≤134 mmol/L) occurring during the study intervention. Secondary outcomes were as follows: (1) severe hyponatremia (plasma sodium level of ≤129 mmol/L or symptomatic hyponatremia), (2) hypernatremia (plasma sodium level of ≥146 mmol/L), (3) plasma ADH levels, (4) adverse events attributable to PMS and/or plasma sodium level derangements occurring within 48 hours after the intervention (Appendix 4), and (5) proportion of patients who changed to open-label PMS during the study period.

### Statistical Analyses

#### Sample Size Calculation

Estimates of a clinically important difference in the primary outcome between the 2 groups were derived from previous literature findings. We calculated that 206 patients would be required to detect a 20% absolute difference in the rate of hyponatremia by using a χ² test, with a 2-sided α level of .05 and statistical power of 80%. With the assumption of 25% loss to follow-up monitoring or inability to measure the primary outcome, the total sample size was increased to 258 (129 patients per group, with the use of a 1:1 allocation ratio). The sample size was calculated by using Power and Sample Size Calculation 2.1.31 software (Vanderbilt University Medical Center, Nashville, TN).

#### Analysis Plan

The statistical analyses of the primary outcome were conducted using a logistic model and the intention-to-treat principle, and then according to the treatment received. We used multiple imputations to handle missing data. Sensitivity analyses were performed for participants for whom complete primary outcome data were available. The results are reported as relative risks (RRs) with 95% confidence intervals (CIs) for binary outcomes, with associated P values. The number needed to treat was also calculated. Subgroup analysis assessing whether admission to the PCCU or the surgical ward affected the primary outcome was conducted by including a treatment group-versus-center type interaction term in the model. For secondary outcomes, categorical data are reported as proportions and continuous data as means ± SDs or medians and ranges, depending on the distribution of the variables. Univariate comparisons for categorical data were performed by using χ² tests or Fisher’s exact tests, if the expected values in any single cell were <5. Continuous data were compared by using t tests or nonparametric Wilcoxon rank tests, if data were skewed. The criterion for statistical significance was set at α = .05. Multiple imputations were conducted by using SAS 9.2 (SAS Institute, Cary, NC). All other analyses were conducted by using Stata 10.2 (Stata Corp, College Station, TX). This study was conducted in accordance with good clinical practice guidelines.

### RESULTS

Between March 2008 and December 2009, 728 consecutive children undergoing elective surgery were screened. Four hundred twenty-seven were eligible and were approached for consent; 159 declined and 258 (60.4% of eligible patients) were enrolled (Fig 1). One hundred twenty-eight patients were assigned randomly to receive isotonic PMS and 130 to receive hypotonic PMS. Four patients in each group were withdrawn after enrollment, 7 on the basis of parents’ requests and 1 on the basis of the physician’s request. There were 10 protocol violations (7 in the hypotonic PMS group and 3 in the isotonic PMS group); 1 patient’s PMS bag was tampered with and unmasked by the bedside nurse, 1 patient received incorrect study fluid for 12 hours, 1 patient received open-label PMS for 5 hours, and the study fluid was discontinued before 48 hours for 7 patients.

Baseline characteristics were similar in the 2 groups (Table 1). Seventy-seven (29.8%) of 258 patients were admitted to the PCCU after surgery. There were no differences in the sodium, EFW, or fluid volume intakes at baseline, before the intervention. Baseline plasma sodium measurements were

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**Note:** The text provided is a summary of the study's methodology and results, focusing on the outcomes and statistical analyses. For a full understanding, refer to the original article in *Pediatrics* Volume 128, Number 5, November 2011, pages 859-869.
ordered by the treating physician in 16 cases (6%). Primary outcome data were available for 218 of the 258 patients. Among the 40 patients for whom plasma sodium level data were not available, 29 cases were attributable to sampling difficulties, 8 patients were withdrawn as described above, and 3 patients were discharged from the hospital early.

The risk of hyponatremia was greater for patients who received hypotonic PMS, compared with isotonic PMS (40.8% vs 22.7%; RR: 1.82 [95% CI: 1.21–2.74]; \( P = .004 \)) (Table 2). Eight patients (6.2%) developed severe hyponatremia following hypotonic PMS, compared with 1 patient (0.8%) in the isotonic PMS group (RR: 7.21 [95% CI: 0.93–55.83]; \( P = .059 \)). Subgroup analysis did not indicate that sicker patients (PCCU admissions) were at increased risk of hyponatremia after adjusting for PMS type (test of interaction: \( P = .105 \)). The risk of hypernatremia was not statistically significantly different between the 2 groups (RR: 1.30 [95% CI: 0.30–5.59]; \( P = .722 \)).

The adverse event rates, PCCU lengths of stay, and hospital lengths of stay were not statistically different between the groups (Table 3). The total volumes of fluid intake during the study period were similar for the 2 groups (Table 4). ADH levels were elevated in both groups on postoperative day 1 but were not statistically different. We performed an exploratory posthoc analysis of data for the subgroup of patients who developed hyponatremia, and we observed elevated ADH levels of 12.51 ± 22.8 pg/mL in patients who received isotonic PMS and 6.01 ± 13.8 pg/mL in patients who received hypotonic PMS.

**DISCUSSION**

The results of this trial demonstrated that the risk of acute postoperative hyponatremia in children was significantly greater with hypotonic PMS, compared with isotonic PMS. The RR reduction for hyponatremia with isotonic PMS was 44.4%. The number-needed-to-treat with isotonic PMS to prevent 1 case of hyponatremia was 6. There was a nonstatistical trend toward increased severe hyponatremia with hypotonic PMS. The concern that isotonic PMS causes hypernatremia was not verified. Although it was hypothesized previously,\(^{21,22}\) patients with greater severity of illness or surgery were not at higher risk of hyponatremia.

It has been suggested that hospital-acquired hyponatremia occurs because of excessive PMS intake and that reduction in the volume of hypotonic PMS would be equally or more effective in preventing hyponatremia than administering isotonic PMS.\(^{23,24}\) However, fluid restriction is potentially deleterious in postoperative patients and delays the normalization of elevated ADH levels.\(^{23,25}\) The PMS intake in this trial was not excessive but were consistent with current maintenance guidelines,\(^{26}\) and was similar in the 2
to excess EFW intake in the form of hypernatremic PMS administration. This conclusion is supported by the urine electrolyte and ADH results. The kidneys regulate water and sodium balances through independent mechanisms, that is, the excretion of water through the distal nephrons (which is inhibited by ADH) and the generation of EFW.\textsuperscript{31} Urinary excretion of a solute load is accompanied by obligate renal generation and absorption of EFW to defend changes in serum osmolality\textsuperscript{32}; therefore, changes in sodium levels typically are analyzed in EFW terms.\textsuperscript{33} To estimate EFW, a calculation is performed in which the solute is excreted in a volume of urine with an isotonic concentration (150 mmol/L) and the balance of the urine volume is thus EFW.\textsuperscript{34} Therefore, for a given urine osmolality, patients who receive hypotonic PMS generate more EFW than those who receive isotonic PMS. This explains how plasma sodium levels were maintained for most patients in this trial and why the majority of patients who received isotonic PMS did not develop hypernatremia. The urine toxicity (Na\textsuperscript{+} + K\textsuperscript{+}) in the hypotonic group indicates that the EFW content was indeed greater than that of the isotonic group. In the presence of increased ADH levels, however, EFW excretion is impaired. In this setting, hypotonic PMS administration would result in a net positive balance in EFW and dilutional hypernatremia, whereas this risk would be reduced with isotonic PMS.

ADH levels often are elevated in postoperative patients, which explains how hypernatremia can develop despite the use of isotonic solutions.\textsuperscript{29} The incidence of hypernatremia after isotonic PMS administration in previous studies ranges from 5% to 20%, depending on the study design and how hypernatremia was defined.\textsuperscript{21,29,34} Key stimuli for ADH secretion are increased serum osmolality, intravascular depletion,
and nonosmotic stimuli. The trend toward higher ADH levels in the isotonic group is explained by the higher osmolar load of 0.9% saline solution. Hyponatremia occurred in 40.8% of patients in the hypotonic group and 22.7% in the isotonic group. We observed elevated ADH levels in these patients, which suggests the contribution of nonosmotic stimuli for ADH in the pathogenesis of hyponatremia. Mean ADH levels were elevated in both groups on postoperative day 1 and normalized the next day. The onset of hyponatremia occurred in the first 24 hours after surgery for the majority of affected patients (59 [80.1%] of a total of 73 patients), which suggests that the risk of hyponatremia may be greatest during this period when ADH secretion is at its peak.

There are a number of strengths of this trial. It is currently the largest randomized trial of its nature with a pediatric surgical population and with an adequate intervention period. The trial was fully blinded and pragmatic, allowing clinicians to adjust fluid administration according to usual care practices and the patient’s clinical status. All caregivers were blinded with respect to study-specific results, to avoid the Hawthorne effect. With the recognition that the symptoms of hyponatremia often are subclinical and with the desire to ensure patient safety, we did not assign a clinical primary outcome. Hyponatremia was chosen as the primary outcome because it is clinically relevant and is acknowledged to be an important surrogate marker for adverse events such as cerebral edema. It reflects a plasma tonicity imbalance and the potential for fluid shifts between intracellular and extracellular compartments. Because hyponatremic encephalopathy in hospitalized children is not uncommon, the trial included a safety algorithm for managing acute plasma sodium level derangements, which allowed a change to open-label PMS without unblinding if it was judged necessary by the treating physician. The proportion of patients who changed to open-label PMS therefore was identified as an important secondary outcome. Allowing clinicians to change to open-label PMS potentially diluted the magnitude of the primary outcome; however, this end point remained statistically significant. Interestingly, more patients in the hypotonic group changed to open-label iso-

### TABLE 4 Electrolyte and Fluid Intake During Study Period

<table>
<thead>
<tr>
<th></th>
<th>Isotonic PMS</th>
<th>Hypotonic PMS</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(N = 128)</td>
<td>(N = 130)</td>
<td></td>
</tr>
<tr>
<td>Total fluid intake,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean ± SD mL/kg per d</td>
<td>mean ± SD mL/kg per d</td>
<td></td>
</tr>
<tr>
<td>Total fluid intake</td>
<td>60.6 ± 33.8</td>
<td>55.6 ± 26.1</td>
<td>1.40</td>
</tr>
<tr>
<td>(intravenous)</td>
<td>0.5 ± 0.26</td>
<td>0.86 ± 0.29</td>
<td>0.237</td>
</tr>
<tr>
<td>Proportion of</td>
<td>1.22 ± 0.46</td>
<td>1.14 ± 0.50</td>
<td>0.02</td>
</tr>
<tr>
<td>calculated TFI, mean</td>
<td>0.04 ± 0.09</td>
<td>0.42 ± 0.10</td>
<td>0.001</td>
</tr>
<tr>
<td>SDs</td>
<td></td>
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<tr>
<td>Total sodium intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mean ± SD mmol/kg per d (n)</td>
<td>mean ± SD mmol/kg per d (n)</td>
<td></td>
</tr>
<tr>
<td>Entire period</td>
<td>6.4 ± 2.8</td>
<td>3.7 ± 1.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>8.1 ± 4.12</td>
<td>4.5 ± 2.7 (126)</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative day 2</td>
<td>5.0 ± 3.1 (106)</td>
<td>3.2 ± 2.8 (102)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total potassium intake</td>
<td>mean ± SD mmol/kg per d (n)</td>
<td>mean ± SD mmol/kg per d (n)</td>
<td></td>
</tr>
<tr>
<td>Entire period</td>
<td>0.4 ± 0.7</td>
<td>0.4 ± 0.6</td>
<td>0.827</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>0.3 ± 0.6 (128)</td>
<td>0.5 ± 0.6 (130)</td>
<td>0.867</td>
</tr>
<tr>
<td>Postoperative day 2</td>
<td>0.3 ± 0.7 (128)</td>
<td>0.2 ± 0.4 (130)</td>
<td>0.325</td>
</tr>
<tr>
<td>Serum ADH level,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(postoperative day 1)</td>
<td>8.0 ± 16.3 (89)</td>
<td>5.53 ± 13.1 (87)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2.7 ± 5.3 (89)</td>
<td>2.4 ± 5.7 (50)</td>
<td>0.818</td>
</tr>
<tr>
<td>Urine sodium level,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(postoperative day 1)</td>
<td>156.8 ± 64.7 (125)</td>
<td>89.0 ± 58.3 (113)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>157.1 ± 63.1 (96)</td>
<td>91.5 ± 57.2 (54)</td>
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</tr>
<tr>
<td>Urine potassium level,</td>
<td>mean ± SD mmol/L (n)</td>
<td>mean ± SD mmol/L (n)</td>
<td></td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>51.1 ± 38.3 (125)</td>
<td>45.3 ± 34.2 (117)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>34.4 ± 24.1 (55)</td>
<td>31.9 ± 24.7 (66)</td>
<td>0.545</td>
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<tr>
<td>Urine tonicity (sodium + potassium),</td>
<td>mean ± SD mmol/L</td>
<td>mean ± SD mmol/L</td>
<td></td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>211.4 ± 70.8</td>
<td>135.0 ± 72.1</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>195.1 ± 65.3</td>
<td>120.6 ± 61.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Urine volume, mean ± SD mL/kg</td>
<td>mean ± SD mL/kg</td>
<td>mean ± SD mL/kg</td>
<td></td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>50.8 ± 31.9</td>
<td>45.0 ± 27.4</td>
<td>0.127</td>
</tr>
<tr>
<td></td>
<td>47.4 ± 32.7</td>
<td>46.4 ± 32.7</td>
<td>0.750</td>
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</tbody>
</table>

All P values are based on t tests.

* TFI indicates actual divided by expected total fluid intake, based on the “4-2-1” calculation. 

* Normal range: 0.5 to 3.5 pg/mL.
totic solutions, with hyponatremia being the most common reason for the change. The lack of differences in adverse events between groups was not surprising, because of the trial design. We recognize the following potential weaknesses. For feasibility reasons, we did not include patients who required emergency surgery, which limits the generalizability of the results for that population, although there is no evidence to suggest that that group of patients might behave differently. Furthermore, exclusion of such patients limits contamination from non-study-related intravenous fluids administered before surgery. Baseline plasma sodium measurements were not stipulated in the protocol for pragmatic reasons, and was therefore only available in a minority of patients. It is not standard practice to measure plasma sodium prior to initiating postoperative fluids, and there is no evidence to suggest that that group of patients might behave differently. Furthermore, exclusion of such patients limits contamination from non-study-related intravenous fluids administered before surgery. Baseline plasma sodium measurements were not stipulated in the protocol for pragmatic reasons, and was therefore only available in a minority of patients. It is not standard practice to measure plasma sodium prior to initiating postoperative fluids, and there is no evidence to suggest that other intraoperative factors in this population would predict differences in plasma sodium at the end of the surgery. Some of the measurements were incomplete because of limitations in sampling. Additional biochemical and osmolality measurements were not conducted because of funding restrictions. However, we thought that it was appropriate to use urine tonicity measurements to support our understanding of the pathogenesis of hyponatremia, because urine tonicity is a better reflection of EFW clearance than urine osmolality.

This trial also reveals the paucity of routine fluid and electrolyte monitoring for surgical patients admitted outside the PCCU. Although 96% of PCCU patients had open plasma sodium measurements in addition to the masked study samples, plasma sodium levels were measured in only 21% of ward patients. Although hyponatremia is the most common electrolyte disorder among hospitalized children, routine electrolyte monitoring in children receiving PMS remains infrequent. Despite heightened awareness and numerous published guidelines, the knowledge transfer of these recommendations currently is inadequate, which partly reflects the limited prospective evidence. The results of this trial, in addition to others, can provide a higher level of evidence and contribute to more-definitive practice recommendations for safe fluid administration in pediatrics.

CONCLUSIONS

Hyponatremia is a common preventable problem among hospitalized children. The results of this trial indicate that the current standard for postoperative fluid and electrolyte management for pediatric patients should change. The findings confirm that ADH levels are elevated in children after surgery and that isotonic PMS is a safer empiric choice for preventing potential harm, compared with hypotonic PMS. However, there is no “ideal” PMS for all children. As with any drug, responses to intravenous fluid therapy should be monitored, and clinicians’ decisions with respect to the most appropriate PMS to use should be individualized and goal-directed.

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APPENDIX 1: SAFETY MONITORING

All masked plasma sodium level results will be reviewed by an independent medical safety officer in real time. Any additional laboratory investigations ordered by the caring physicians or surgeons will be their responsibility to review. If blinded plasma sodium levels fall within the predefined safety thresholds for hyponatremia or hypernatremia (plasma sodium levels of <133 or >147 mmol/L, respectively), the physicians will be notified and will be prompted to assess their patient and to refer to the clinical pathways for managing acute plasma sodium level derangements (Appendices 2 and 3), if necessary. The actual results will not be given to them unless the values are in the “severe” range (ie, plasma sodium levels of <130 or >150 mmol/L).

The clinical pathways serve as guidelines only. The goal is to encourage and to enable clinicians to assess the patient’s clinical status and to individualize fluid therapy according to their best judgment and usual practice. Dictating what a clinician does without knowledge of the patient’s assessment results is not in keeping with clinical practice and obscures the generalizability of the study results.

APPENDIX 4: TRIAL-SPECIFIC ADVERSE EVENTS

An adverse event is defined as any undesirable experience that occurs to a clinical study participant that is unrelated to the patient’s underlying condition, diagnosis, or surgical procedure. Adverse events were evaluated through blinded assessments during the study period and for 48 hours after study fluid administration was discontinued or until patient discharge, whichever occurred first. Potential anticipated adverse events included (1) clinical evidence of extracellular volume overload developing after the institution of study fluid administration, as defined by the presence of new-onset, generalized, peripheral edema associated with daily weight gain and/or tachypnea, tachycardia, hypoxia, pulmonary crepitations, and pul-

APPENDIX 2

Clinical pathway for hyponatremia. PNa indicates plasma sodium level.

APPENDIX 3

Clinical pathway for hypernatremia. PNa indicates plasma sodium level.
monary congestion on chest radiographs, (2) seizures of new onset (among patients without a preexisting seizure disorder), (3) acute cerebral edema, defined on the basis of an altered level of consciousness, with or without associated changes in cardiorespiratory status, and consistent computed tomographic scan findings, (4) new-onset persistent hypertension, defined as systolic blood pressure of >95th percentile for age or any blood pressure requiring antihypertensive medication, and (5) admission to the PCCU because of sequelae of fluid and electrolyte abnormalities occurring during the study period.

An adverse event was considered serious if it was life-threatening, prolonged patient hospitalization, was considered medically important, or resulted in persistent or significant disability or incapacity or death. The relationship of the adverse events and serious adverse events to the study intervention was determined through blinded assessments by the most responsible physician, and findings were reviewed by the principle investigator and the data safety monitoring committee. The data safety monitoring committee performed periodic reviews of all adverse events and trial conduct.

**DIGITAL IMPRESSIONS:** Two of my children are still in high school. One, a senior, is applying to college, while the other, a junior has already begun her search. We have spent a fair amount of time deciding to whom the ACT or SAT scores should be sent and whether they should attend a showcase soccer or lacrosse camp to impress one of the coaches. What we have not discussed nearly enough is what has been posted on their Facebook pages. As reported in USA Today (Education: September 22, 2011), college admissions officers frequently search social media for information about applicants. Approximately ¼ of admissions officials at 359 selective colleges reported that they viewed Facebook pages while 20 percent performed a Google search to learn more about applicants. While the practice is still controversial, some schools forbid admission officers from performing such a search, schools that conduct searches report that students live in a social world and that anything posted can contribute in a positive or negative way to the student’s application. Unfortunately, for 12 percent of applicants, what was posted on social media negatively impacted their chance for admission. Findings that hurt applicants included vulgar language, photographs of underage drinking, and evidence of plagiarism. Admission officials will also act on tips about inappropriate postings. For example, one school rejected an applicant because she had posted explicit pictures of herself. While it is unclear how many applicants benefitted from what is posted on social media, some college admission officials evaluate the student’s digital literary skills. Students with a strong digital presence can be considered more highly qualified. As for me, with some trepidation, I performed a brief Google search on my two children. I was much relieved only to see a pretty funny picture of my son with three of his friends on his Facebook page. Still, we will have a conversation about posting to social media and making sure that they know that whatever is posted can be found and viewed by others.

Noted by WVR, MD