Peer Reviews Comments

Advisor's Consolidated Report on Raychel Ferguson.

Northern Ireland Inquiry into Hyponatraemia Related Deaths

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I have read the Advisor's Consolidated report dated 28th February 2013 on Raychel Ferguson, as well as the opinions of some of the inquiry's experts. In particular I have reread the expert reports provided by Drs Scott-Jupp, Hayes and Sally Ramsey.

The report is very comprehensive and highlights the key issues. I do have a few issues that I would like to highlight. Many of the themes and issues have much in common with those highlighted in their report on Lucy Crawford.

1. Communication

The issues about poor communication come through even more strongly in this case across all disciplines and at all levels. There was poor communication within the surgical team from the time of Raychel's admission to her medical crisis in the early hours of 9th June. She was taken to the operating room by a surgical trainee without the knowledge of the consultant who was responsible for her care. The same applies to the anaesthetic trainees. There was confusion about who was responsible for ordering the post operative fluids. The anesthetists thought it was the surgeons and while the surgeons recognized that it was their responsibility the reality was that the nurses were deciding what iv fluid should be given and asking the paediatric trainees to write the prescription. The communication both within surgical trainee group and with the consultant was also poor. There was no system for a formal ward round to review emergency admissions from the previous night. The responsible surgeon was not informed about Raychel's crisis on 9th June. He also did attend the meeting with the family arranged by the chief executive officer in August.

I would also highlight poor communication between the ward nurses and Raychel's parents whose concerns about her increasing lethargy and vomiting don't seem to have been given sufficient attention. One of the major issues in this case is Raychel's post operative vomiting, both in terms of it's severity and cause because it was a major contributor to her hyponatraemia. The parents describe frequent large amounts of vomitus. The nurses have a different recollection and did not agree with the parent's concern. Given the subsequent events I am more likely to subscribe to the parent's version of events. One of the most important lessons in paediatric practice is always listen to the parents. Their concerns may not always be well founded but they are more often right that not.

The communication between the parents and the hospital leadership in Altnagelvin was also less than optimal. They did not provide full disclosure as to the cause of Raychel's death from hyponatraemia. Finally, I would again question RBHSC's leadership role in disseminating information about adverse outcomes from iv hypotonic saline which also comes under the

heading poor communication. I raised this issue in my comments in my previous report on Lucy Crawford. I don't see evidence of RBHSC discussing this Altnagelvin. However, Dr. Nesbitt should be commended for taking the lead on this.

2. Medical and nursing knowledge, understanding of iv fluids and their administration in children

Raychel's case has some unique features which set it apart from the other cases reviewed by the inquiry in that the hyponatraemia was caused by a combination of hypotonic saline administered as maintenance fluid, albeit is excessive amounts, and major gastrointestinal losses of sodium from severe vomiting. Adam Strain was also a surgical patient but in his case excessive amounts of hypotonic saline were given on the assumption that he had accumulated a fluid deficit.

Stomach and intestinal contents have a sodium concentration in the range of 90-100 mmol/l. Solution 18 contains 30 mmol/l of sodium. So here we have a potentially deadly combination of excessive water being administered when a patient is losing a large amount of sodium. The only possible result is the development of acute hyponatraemia. The only expert's report that has correctly identified this as the underlying cause is the one submitted by Dr. Simon Hayes. Other reports refer to excessive iv maintenance fluids which was only part of the problem. Standard surgical teaching is that you replace GI losses with 0.9NaCl. It is suprising and concerning that this was not clearly understood on a paediatric ward that cared for surgical patients. Nurses caring for surgical patients should have been aware of this, an opinion endorsed by Susan Chapman in her expert opinion report (098-92-334).

The issue of what was the state of knowledge of fluid and electrolyte physiology in 2001 is a recurring theme. It is repeatedly stated that it is part of the medical and nursing curriculum. However, there is clearly a gap between what people were expected to know and what they actually knew. There are important references in the published literature (attached) which address this topic, one published in 1997 and one in 2000. Both are questionnaires from the UK and address the level of understanding of perioperative fluid management among trainees in surgery and anaesthesia.

Lobo *(Clin Nutrition 2001; 20:125)* surveyed JHOs and SHOs in surgery about fluid prescribing practices and relevant knowledge in surgical patients. The author's state in their introduction

that *"although the prescription of fluid and electrolytes is an integral part of perioperative care in surgical patients, this is usually is left to the most junior members of the team who lack the knowledge and experience to undertake this task competently."* Their study supports this hypothesis. Only 40% of respondents could correctly identify the correct concentration of sodium in solution 18 to within 5% of the actual level. Over 60% said they had been given no formal or informal guidelines on fluid and electrolyte prescribing when joining the surgical rotation. I suspect that if these surveys had extended up to consultant level the results would not have been that much different. They don't usually write fluid orders.

The second paper by *White (Anaesthesia 1997; 52:422)* conducted a survey of anaesthesia trainees asking them to identify the electrolyte composition of Hartmann's solution. The results make equally dismal reading.

These findings are illustrative of the state of knowledge of fluid and electrolyte physiology among physicians practicing in the UK and caring for a surgical population around the time of Raychel's death. I also think that it is noteworthy that the only two doctors (Makar and Gund) who prescribed Hartmann's solution, which is the correct type of fluid for perioperative care, both trained outside the UK. Both were persuaded to change their orders because they didn't conform to local practice.

I have read several references in the various experts' reports about junior trainees seeking advice from more senior colleagues when Raychel was deteriorating. Clearly the problem of her vomiting required more attention that it got but I would not be confident that, given the state of knowledge at the time, that the significance of this would have been appreciated and the appropriate action taken in revising the fluid order.

I have also read in various reports submitted by paediatric experts that acute hyponatraemia is a very rare event. I don't think that statement stands close scrutiny. Acute *symptomatic* hyponatraemia is a rare event but probably under recognized. By this I mean children with hyponatraemia and neurological symptoms, which don't usually occur until the level falls below 125 mmol/l. We don't know the true incidence of hyponatraemia without symptoms because there are no published observational studies published in children receiving 0.18 saline where regular measurements of serum sodium have been made. We also have to accept that failure to recognize that seizures and coma in children receiving hypotonic saline is a common theme that recurs in published case reports. In addition, this publication bias means that there are many more cases that are not reported – people didn't like to expose their errors. So, paediatricians who have used hypotonic saline in their practice and never seen a case have more than likely not made the connection. Also, they are not dealing with a surgical population.

What I can say with some certainty is that acute asymptomatic hyponatraemia is common in a paediatric surgical population where hypotonic saline is used as a post operative maintenance fluid. The paper by *Eulmesekian (Pediatr Crit Care Med 2010*), in which I was a co-author, found a 20% incidence of hyponatraemia (sodium <135 mmol/l) in 81 children following surgery receiving saline with a sodium concentration of 40 mm/l). A similar percentage was found in Choong's paper *(Choong Pediatrics 2011)* where she compared the sodium values in children receiving 0.9 saline with 0.45 saline, which is hypotonic with a saline concentration of 75 mmol/l. In neither of these studies, in which there were a total of 210 children who received hypotonic fluid, was there a single neurological event observed because the level did not fall far enough or fast enough to produce symptoms. However, they all fitted the definition of acute hyponatraemia.

Finally, there has been a considerable discussion about the knowledge and understanding of iv fluids and their administration in children. Equally important is the issue of the diagnosing and treating acute symptomatic hyponatraemia and the leading role taken in this area by the health service in Northern Ireland needs to be recognized. Hopefully with this initiative the number of cases in future will be truly rare. Acute symptomatic hyponatraemia is a genuine medical emergency where minutes count in order to prevent brain stem coning. Failure to recognize and expeditiously treat the problem is a common theme in many of the case published reports. Principle among these is not believing and then repeating a blood test showing a very low sodium value, ascribing it to "lab error." Labs rarely make errors. Their analyzers are regularly calibrated. They accurately measure the samples they are sent. Valuable time can be lost in initiating treatment. I noted that in Raychel's case 3% saline, the preferred treatment for raised intracranial pressure in association with hyponatraemia, was not readily available. However, mannitol can be equally effective in a crisis. It would be important that hospitals treating children have an explicit protocol for treating acute symptomatic hyponatraemia as well as a strategy for preventing it.

3 The responsible physician (surgeon) at Altnagelvin Hospital.

This is a similar theme which was highlighted in Lucy's case. Clearly this was also a problem in Raychel's care. There has to be a clear understanding that a patient is admitted under the care of a consultant physician or surgeon who is responsible for their care and parents should be informed who that individual is. When untoward events occur he or she has an obligation to meet with the family and provide an explanation.

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

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Objective: **To establish the prevalence 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: **Prevalence 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 prevalence of hyponatremia at 12 hrs was 17 (21%) of 81 (95% confidence interval, 3.7–38.3); at 24 hrs, it was 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 prevalence 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; 11:000–000)**

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

Acute severe hyponatremia, defined as a reduction in plasma sodium (PNa) to <130 mmol/L, is increasingly recognized as a cause of morbidity and mortality in hospitalized patients. Children are particularly at risk because of the widespread perioperative use of hypotonic solutions administered as maintenance fluids to replace urine output and insensible losses in patients unable to take oral fluids. The formula used in the calculation that established the use of hypotonic saline in pediatric practice was developed by Holliday and 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 prevalence 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 prevalence 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) be-

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tween 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 Risk of Mortality Score (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 *in situ*; and f) fluid intake and output.

PNa and plasma potassium were measured in our central laboratory by indirect potentiometry with two ion selective electrodes, using a Synchron 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 urine 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).

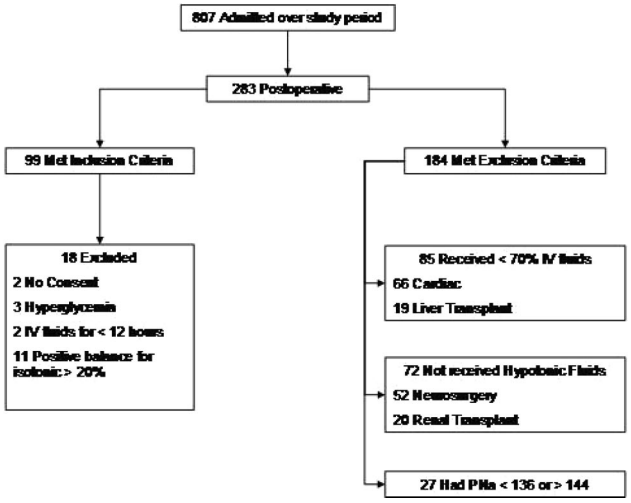

Figure 1. Patients' flow diagram.

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.

Table 1. Patient demographics (n = 81 patients)

Age, yrs (mean ± SEM)	9.78 ± 0.69
Mortality Predicted by PIM2 in % (mean ± SEM)	1.12 ± 0.29
LOS, days (mean ± SEM)	1.81 ± 0.08
Weight, kg (mean ± SEM)	34.6 ± 2.44
Gender, n (%)	F 45 (55.6)/ M 36 (44.4)
Ventilated, n (%)	13 (16)
General surgery, n (%)	34 (42)
Orthopedic surgery, n (%)	31 (38.3)
Thoracic surgery, n (%)	13 (16)
Plastic Surgery, n (%)	3 (3.7)
0–10 kg	19 (23)
10–20 kg	11 (14)
20–30 kg	7 (9)
30–40 kg	12 (15)
40–50 kg	9 (11)
50–60 kg	14 (17)
>60 kg	9 (11)

PIM2, Pediatric Index of Mortality 2; LOS, length of stay.

The prevalence 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 between the prevalence of hyponatremia in ventilated patients (n = 5 of 13 or 38%) (95% CI, 3.6–72.4) and nonventilated patients (27 of 68 or 39%) (95% CI, 24.6–53.4).

Univariate analysis of variables at two time points, 12 hrs and 24 hrs, in hyponatremic and isonatremic patients is reported in Tables 2 and 3.

At 12 hrs, relative risks of hyponatremia were 11.55 (95% CI, 2.99–44.63; $p = .0004$) for an Na loss >0.5 mmol/kg/hr, 10 (95% CI, 2.55–39.15; $p = .0009$) for a negative Na balance >0.3 mmol/kg/hr, and 4.25 (95% CI, 1.99–9.08; $p = .0002$) for a urine output >3.4 mL/kg/hr.

At 24 hrs, relative risk for hyponatremia was 3.25 (95% CI, 1.2–8.77; $p = .0201$) for a positive fluid balance of >0.2 mL/kg/hr.

DISCUSSION

This study shows that the prevalence of hospital-acquired hyponatremia in this population of postoperative patients, admitted to the PICU and who received maintenance fluids in the form of hypotonic saline in accordance with the standard recommendations, was high and increased over time—namely, it was 21% (95% CI, 3.7–38.3) at 12 hrs and 31% (95% CI, 11.4–50.6) at 24 hrs. This adds to the increasing body of evidence that suggests that hyponatremia associated with the use of hypotonic saline is a common event and places children at risk for cerebral edema even after minor surgical procedures, such as tonsillectomy (5, 10).

The prevalence 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 hypotonic 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 hours. 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 isonatramic (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 sur-

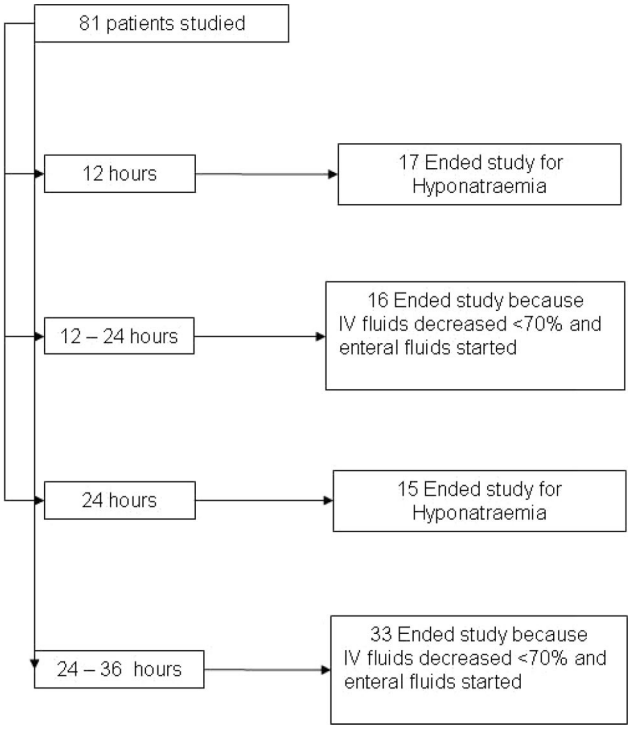

Figure 2. Timeline of study patients.

Table 2. Univariate analysis of variables studied at 12 hrs

	Isonatremic			Hyponatremic					
Variable	n	Mean	SEM	n	Mean	SEM	Diff	95% CI	*p*
Age, yrs	64	9.75	0.76	17	9.89	1.70	0.14	−3.28 to 3.56	.9349
Weight, kg	64	35.64	2.77	17	30.71	5.19	−4.93	−16.91 to 7.04	.4146
PNa 0 hs (mmol/L)	64	139.59	0.27	17	138.65	0.54	−0.95	−2.13 to 0.23	.1154
PNa 12 hs (mmol/L)	64	138.03	0.24	17	133.35	0.42	−4.68	−5.70 to −3.65	<.0001
Hypot Fl In (mL/kg/hr)	64	2.61	0.15	17	3.17	0.39	0.56	−0.13 to 1.26	.1145
Urine (mL/kg/hr)	64	2.20	0.11	17	3.08	0.33	0.87	0.31 to 1.43	.0026
Fl Bal (mL/kg/hr)	64	0.16	0.12	17	−0.31	0.23	−0.47	−1.01 to 0.06	.0859
Na In (mmol/kg/hr)	64	0.22	0.01	17	0.25	0.03	0.03	−0.02 to 0.08	.3080
Na Out (mmol/kg/hr)	25	0.34	0.02	10	0.62	0.07	0.28	0.15 to 0.40	.0001
Na Bal (mmol/kg/hr)	25	−0.13	0.02	10	−0.39	0.05	−0.26	−0.36 to −0.16	<.0001
UNa+UK (mmol/L)	25	178.16	13.66	10	194.30	14.53	16.1	−31.84 to 64.12	.4985

Considering insensible losses that were calculated in 14 mL/kg/day [16]; 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.

Table 3. Univariate analysis of variables studied at 24 hrs

Variable	Isonatremic			Hyponatremic					
	n	Mean	SEM	n	Mean	SEM	Diff	95% CI	*p*
Age, yrs	33	9.96	1.08	15	9.05	1.60	−0.92	−4.80 to 2.97	.6374
Weight, kg	33	37.39	4.00	15	28.20	5.21	−9.19	−23.09 to 4.70	.1897
PNa 0 hs, mmol/L	33	139.58	0.39	15	139.07	0.54	−0.51	−1.90 to 0.88	.4674
PNa 12 hs, mmol/L	33	138.61	0.31	15	136.53	0.19	−2.07	−3.04 to −1.09	.0001
PNa 24 hs, mmol/L	33	138.21	0.32	15	134.40	0.68	−3.81	−5.14 to −2.47	<.0001
Hypot Fl In, mL/kg/hr	33	2.56	0.20	15	2.97	0.31	0.40	−0.35 to 1.15	.2872
Urine, mL/kg/hr	33	2.23	0.14	15	2.12	0.24	−0.11	−0.64 to 0.42	.6716
Fl Bal, mL/kg/hr	33	0.10	0.14	15	0.65	0.23	0.55	0.027 to 1.072	.0396
Na In, mmol/kg/hr	33	0.22	0.02	15	0.29	0.02	0.07	0.007 to 0.13	.0294
Na Out, mmol/kg/hr	15	0.31	0.03	6	0.43	0.07	0.13	−0.005 to 0.25	.0586
Na Bal, mmol/kg/hr	15	−0.11	0.03	6	−0.17	0.02	−0.05	−0.17 to 0.062	.3485
UNa+UK 0–12 hs, mmol/L	15	154.47	17.92	6	216.00	25.87	61.53	−7.11 to 130.18	.0761
UNa+UK 12–24 hs, mmol/L	15	141.00	15.64	6	138.17	12.77	−2.83	−59.14 to 53.47	.9175

Considering insensible losses that were calculated in 14 mL/kg/day [16]; 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.

gical 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 antiduretic 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 hypotonic 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 after 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 surgical procedures and may represent a group particularly at risk. Burrows and colleagues (23), in a controlled trial of postoperative fluids, compared hypotonic saline and Ringer's lactate. Both groups had a fall in PNa, which was more significant in those receiving hypotonic 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 hypotonic 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 failed to produce dilute urine, clear evidence that there was nonphysiologic secretion of antiduretic hormone. Patients with scoliosis may also be particularly at risk because the blood loss is usually considerable and, therefore, the amount of intraoperative fluids administered may lead to volume overexpansion and a setup for desalination.

Our study provides further evidence that the use of hypotonic saline, as suggested by Holliday and Segar's formula for maintenance fluids in postoperative management, is associated to a high occurrence rate of acute hyponatremia. Despite an increasing number of publications 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 hypotonic 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 isotonic 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 PNa levels beyond 24 postoperative hours.

In conclusion, the prevalence of hospital-acquired hyponatremia in this population of postoperative patients admitted to the PICU and who received maintenance fluids in the form of hypotonic saline in accordance with the standard recommendations, was high and progressive over time. Negative Na balance in the first 12 hrs and a positive fluid balance could be major contributors to the development of hyponatremia in postoperative patients. This raises the question as to whether the use of isotonic saline in lesser amounts than currently recommended for maintenance requirements would be a better choice.

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

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

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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

This trial has been registered at www.clinicaltrials.gov (identifier NCT00734214) and www.controlled-trials.com/isrctn (identifier ISRCTN11597444).

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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. *Pediatrics* 2011;128:857–866

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] translocational 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 hypernatremia, interstitial fluid overload, excessive sodium excretion, and hyperchloremic metabolic acidosis.[14–16] The primary objective of this fully blinded, randomized 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 research 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 preexisting 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 (eg, potassium chloride concentration), and the patient's name (after random assignment). Fluids were administered intraoperatively 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 (Appendixes 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.[17]

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.[18,19] We calculated that 206 patients would be required to detect a 20% absolute difference in the rate of hyponatremia by using a χ^2 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.[20] 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-ward 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 χ^2 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 $\alpha = .05$. 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

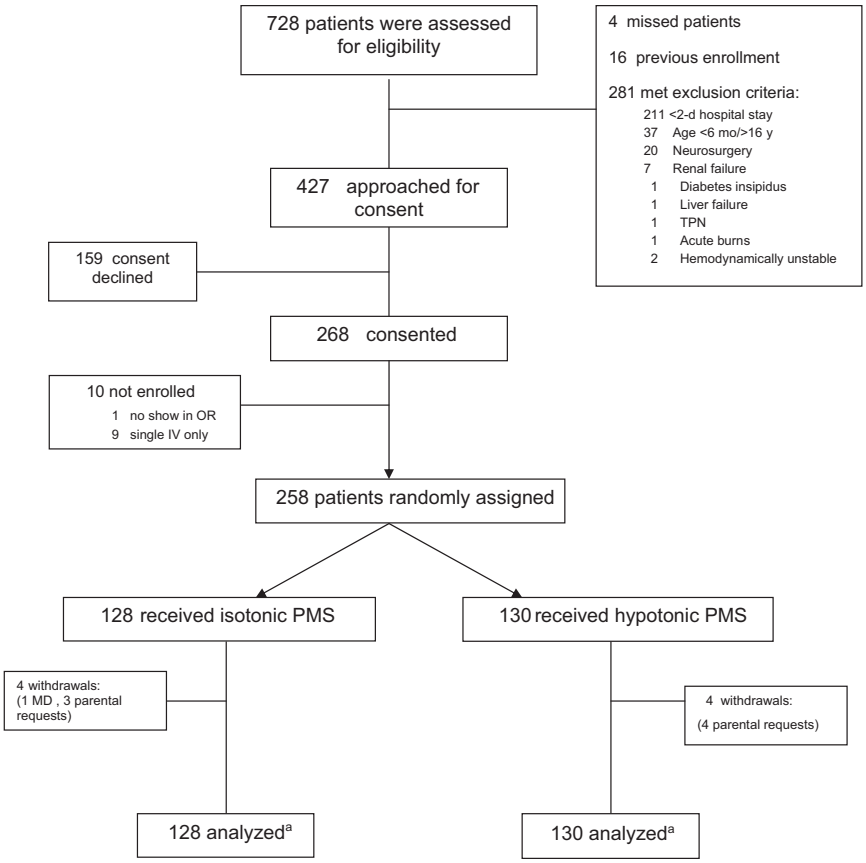

FIGURE 1

Enrollment and outcomes. TPN indicates total parenteral nutrition; OR, operating room; MD, physician; IV, intravenous. [a] Data on the primary outcome were available for 106 patients in the isotonic group and 112 patients in the hypotonic group.

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 sensitivity analysis using complete data revealed similar results (Table 2).

A total of 24 (9.3%) of 258 patients changed to open-label PMS during the study period (Table 3), 17 (13.1%) from the hypotonic PMS group and 7 (5.5%) from the isotonic PMS group ($P = .059$). More patients who received hypotonic PMS changed to open-label isotonic solutions (9.2% vs 2.3%; $P = .036$), with hyponatremia being the most commonly stated reason for the change (5.4% vs 0.8%; $P = .033$). 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 ± 13.6 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.[8,22,25] The PMS intake in this trial was not excessive but were consistent with current maintenance guidelines,[26] and was similar in the 2

TABLE 1 Baseline Characteristics

Characteristic	Isotonic PMS ($N = 128$ [49.6%])	Hypotonic PMS ($N = 130$ [50.4%])
Age, mean ± SD, y	9.2 ± 5.5	9.2 ± 5.7
Weight, mean ± SD, kg	36.0 ± 23.0	38.6 ± 26.8
Male, *n* (%)	53 (41.4)	62 (47.7)
Postoperative admission location, *n* (%)		
Surgical ward	85 (68.0)	94 (72.3)
PCCU	41 (32.0)	36 (27.7)
PRISM III score for PCCU patients, mean ± SD	3.2 ± 3.0	2.5 ± 2.3
Type of surgery, *n* (%)		
Orthopedic	56 (43.8)	56 (43.1)
General	25 (19.5)	21 (16.2)
Urologic	17 (13.3)	21 (16.2)
Plastic	15 (11.7)	16 (12.3)
Ear/nose/throat	7 (5.5)	12 (9.2)
Craniofacial	6 (4.6)	2 (1.5)
Maxillofacial	2 (1.6)	2 (1.5)
Duration of surgery, median (range), h		
All patients	3.58 (0.8–14.5)	3.43 (0.8–15.6)
PCCU patients	8.83 (0.6–14.5)	8.08 (0.8–15.6)
Surgical ward patients	3.07 (0.8–8.3)	3.08 (0.9–7.5)
Baseline parameters (at end of surgery)		
Proportion of EFW intake, mean ± SD[a]	0.03 ± 0.05	0.03 ± 0.06
Sodium intake, mean ± SD, mmol/kg	5.2 ± 4.5	5.2 ± 5.4
Fluid intake, mean ± SD, mL/kg	40.0 ± 41.7	39.8 ± 51.6
Time from end of surgery to study intervention, median (range), min	22 (0–300)	22 (0–315)
Duration of study intervention, median (range), h		
All patients	48 (0.2–70)	47.2 (0.3–64.9)
PCCU patients	48 (0.2–70)	48 (5–63)
Surgical ward patients	48 (1.5–61.7)	46.2 (0.3–64.9)
Baseline plasma sodium level, mean ± SD, mmol/L[b]	140 ± 2.2	138 ± 3.2

PRISM III indicates Pediatric Risk of Mortality III.

[a] EFW intake calculation: [154 − (sodium level/total volume, in liters)]/154.

[b] Baseline plasma sodium levels were measured for 7 patients in the isotonic group and 9 patients in the hypotonic group.

TABLE 2 Primary and Key Secondary Outcomes

	Isotonic PMS	Hypotonic PMS	RR (95% CI)	*P*
Intention-to-treat analysis after 10 imputations, *N*	128	130	—	—
Hyponatremia, *n* (%)	29 (22.7)	53 (40.8)	1.82 (1.21–2.74)	.004
Severe hyponatremia, *n* (%)	1 (0.8)	8 (6.2)	7.21 (0.93–55.83)	.059
Hypernatremia, *n* (%)	4 (3.1)	5 (3.9)	1.30 (0.30–5.59)	.722
Sensitivity analysis using complete data only, *N*	106	112	—	—
Hyponatremia, *n* (%)	26 (24.5)	47 (42.0)	1.78 (1.18–2.69)	.006
Severe hyponatremia, *n* (%)	1 (0.9)	7 (6.3)	6.63 (0.83–52.93)	.075
Hypernatremia, *n* (%)	3 (2.8)	4 (3.3)	1.26 (0.29–5.51)	.757

groups. These results argue against the traditional recommendations to match parenteral sodium intake to dietary requirements in the acute postoperative period,[27] and they support emerging evidence that the tonicity of PMS has a greater effect on plasma sodium levels than does the volume of PMS administration.[22,28,29] Hyponatremia occurs because of a deficit in sodium or a positive balance of EFW.[30] The sodium intakes in both groups in this trial were well within the suggested daily requirements[26]; therefore, hyponatremia is not explained by inadequate intake or total-body sodium depletion. We conclude that the risk of hyponatremia was attributable to excess EFW intake in the form of hypotonic 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.[31] Urinary excretion of a solute load is accompanied by obligate renal generation and absorption of EFW to defend changes in serum osmolality[32]; therefore, changes in sodium levels typically are analyzed in EFW terms.[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.[33] 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 tonicity ($Na^+ + K^+$) 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 hyponatremia, whereas this risk would be reduced with isotonic PMS.

ADH levels often are elevated in postoperative patients, which explains how hyponatremia can develop despite the use of isotonic solutions.[29] The incidence of hyponatremia after isotonic PMS administration in previous studies ranges from 5% to 20%, depending on the study design and how hyponatremia was defined.[21,29,34] Key stimuli for ADH secretion are increased serum osmolality, intravascular depletion,

TABLE 3 Secondary Outcomes

	Isotonic PMS ($N = 128$)	Hypotonic PMS ($N = 130$)	*P*
Changed to open-label PMS, *n* (%)	7 (5.5)	17 (13.1)	.059
Isotonic PMS	3 (2.3)	12 (9.2)	.036
Hypotonic PMS	3 (2.3)	5 (3.9)	.736
TPN	1 (0.8)	0 (0.0)	.994
Time to change to open-label PMS, median (range), h	30.9 (2.7–55.4)	22 (5.7–42.0)	.874
Stated reason for change to open-label PMS, *n* (%)			
Hyponatremia	1 (0.8)	7 (5.4)	.033
Hypernatremia	1 (0.8)	1 (0.8)	.991
Other[a]	4 (3.1)	9 (6.9)	.163
Adverse events, *n* (%)	9 (7.0)	10 (7.7)	.359
Generalized edema	9 (7.0)	8 (6.2)	—
New-onset hypertension	0 (0.0)	2 (2.8)	—
PCCU length of stay, median (range), h	44.8 (4.1–435.2)	45.8 (15.9–1961.9)	.258
Hospital length of stay, median (range), d	3 (0–131)	3 (0–235)	.728

P values were based on χ^2 tests for categorical variables and Wilcoxon rank tests for continuous variables. TPN indicates total parenteral nutrition.

[a] Other indicates parenteral nutrition, protocol violation, hemodynamic instability, or hypokalemia.

TABLE 4 Electrolyte and Fluid Intake During Study Period

	Isotonic PMS ($N = 128$)	Hypotonic PMS ($N = 130$)	*P*
Total fluid intake, mean ± SD, mL/kg per d	60.6 ± 33.8	55.6 ± 29.1	.140
Total fluid intake (intravenous) as proportion of calculated TFI, mean ± SD[a]	0.91 ± 0.26	0.86 ± 0.29	.237
Total fluid intake (oral and intravenous) as proportion of calculated TFI, mean ± SD[a]	1.22 ± 0.46	1.14 ± 0.50	.207
Proportion of EFW intake, mean ± SD	0.04 ± 0.09	0.42 ± 0.10	<.001
Total sodium intake, mean ± SD, mmol/kg per d (*n*)			
Entire period	6.4 ± 2.8	3.7 ± 1.9	<.001
Postoperative day 1	8.1 ± 4.4 (126)	4.5 ± 2.7 (126)	<.001
Postoperative day 2	5.0 ± 4.3 (106)	3.2 ± 2.8 (102)	<.001
Total potassium intake, mean ± SD, mmol/kg per d (*n*)			
Entire period	0.4 ± 0.7	0.4 ± 0.6	.827
Postoperative day 1	0.3 ± 0.6 (128)	0.3 ± 0.6 (130)	.867
Postoperative day 2	0.3 ± 0.7 (128)	0.2 ± 0.4 (130)	.325
Serum ADH level, mean ± SD, pg/mL (*n*)[b]			
Postoperative day 1	8.0 ± 16.3 (89)	5.3 ± 13.1 (97)	.208
Postoperative day 2	2.7 ± 5.3 (59)	2.4 ± 5.7 (50)	.818
Urine sodium level, mean ± SD, mmol/L (*n*)			
Postoperative day 1	156.8 ± 64.7 (125)	89.0 ± 58.3 (113)	<.001
Postoperative day 2	157.1 ± 63.1 (69)	91.5 ± 57.2 (54)	<.001
Urine potassium level, mean ± SD, mmol/L (*n*)			
Postoperative day 1	51.1 ± 38.3 (125)	45.3 ± 34.2 (117)	.220
Postoperative day 2	34.4 ± 24.1 (59)	31.9 ± 24.7 (66)	.545
Urine tonicity (sodium + potassium), mean ± SD, mmol/L			
Postoperative day 1	211.4 ± 70.8	135.0 ± 72.1	<.001
Postoperative day 2	195.1 ± 65.3	120.6 ± 61.5	<.001
Urine volume, mean ± SD, mL/kg			
Postoperative day 1	50.8 ± 31.9	45.0 ± 27.4	.127
Postoperative day 2	47.4 ± 32.7	46.4 ± 32.7	.750

All *P* values are based on *t* tests.

[a] TFI indicates actual divided by expected total fluid intake, based on the "4-2-1" calculation.[1]

[b] Normal range: 0.5 to 3.5 pg/mL.

and nonosmotic stimuli.[35,36] 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 a Hawthorne effect.[37] 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.[16,38] It reflects a plasma tonicity imbalance and the potential for fluid shifts between intracellular and extracellular compartments.[39] Because hyponatremic encephalopathy in hospitalized children is not uncommon,[38] 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-

tonic 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,[40,41] 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.[32]

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,[4,42] routine electrolyte monitoring in children receiving PMS remains infrequent.[41,43] Despite heightened awareness and numerous published guidelines,[44] the knowledge transfer of these recommendations currently is inadequate, which partly reflects the limited prospective evidence.[43] 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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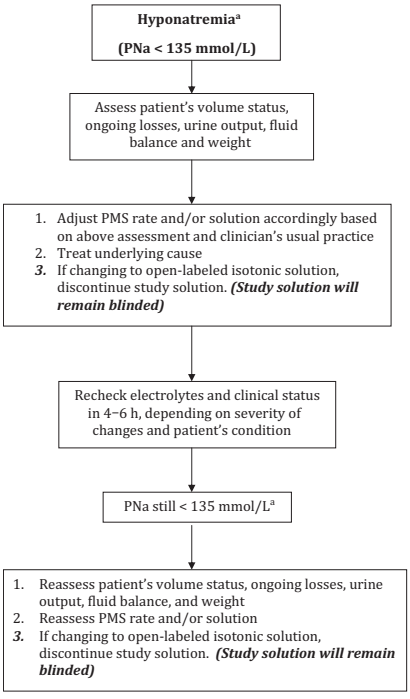
APPENDIX 1: SAFETY MONITORING

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 (Appendixes 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).

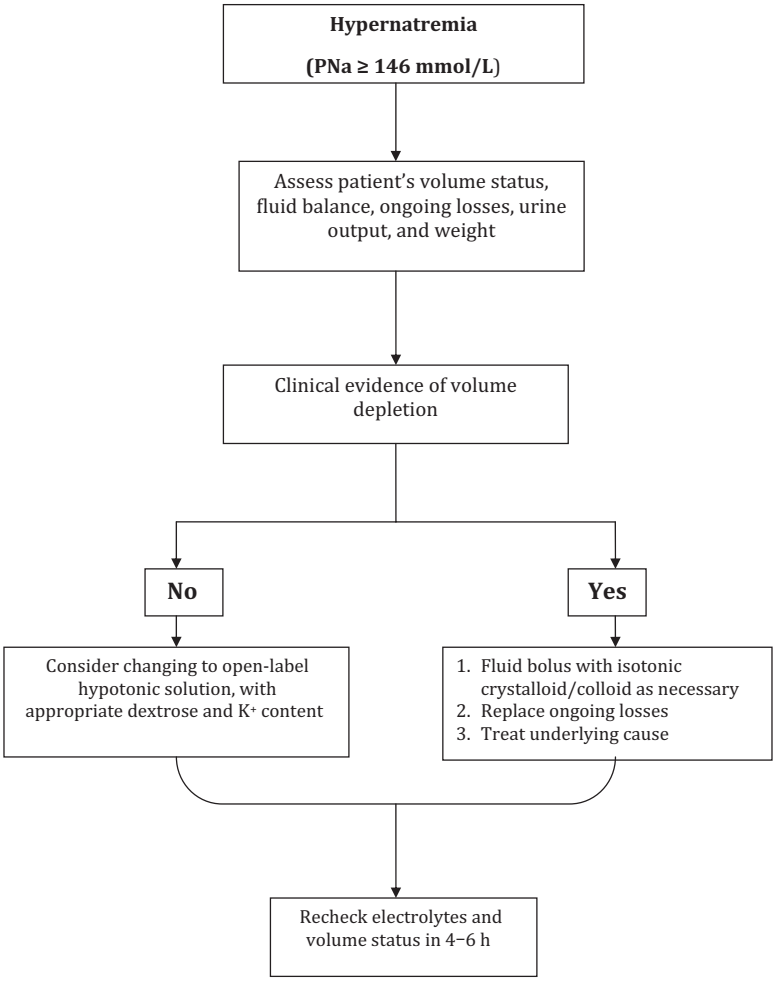
The clinical pathways serve as guidelines only. The goal is to encourage and to enable clinicians to assess the patient's clinical status and to individualize fluid therapy according to their best judgment and usual practice. Dictating what a clinician does without knowledge of the patient's assessment 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. [a] If the patient has severe hyponatremia, defined as a PNa level of <130 mmol/L, and/or the patient is symptomatic (seizures, decreased level of consciousness, coma), administration of hypertonic saline (3% NaCl) should be considered. Hypertonic saline should be administered to patients who develop acute symptomatic hyponatremia, and the PCCU physician and/or nephrologist should be consulted.



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.

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

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Is Hartmann's the solution?

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Summary

As Hartmann's solution is commonly used by anaesthetists, we surveyed a group of Part III FRCA candidates to establish their knowledge of its constituents and the purpose and metabolism of the lactate in solution. Of the 82 candidates surveyed only three (4%) accurately recorded the electrolytes and their concentrations in Hartmann's solution. Lactate was stated to be a source of bicarbonate by 52 (63%) and a source of glucose by 17 (21%). The descriptions of lactate metabolism were largely imprecise, none was complete and 24 (29%) of candidates offered no explanation. The constituents of Hartmann's solution and their concentrations are designed to match those of plasma, reducing ion and fluid shifts postinfusion. The lactate in Hartmann's solution is metabolised by both oxidation and gluconeogenesis, predominantly in the liver, and bicarbonate is generated by both processes over 1–2 h.

Keywords *Fluid balance*; Hartmann's solution. *Metabolism*; lactate.

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Accepted: 18 November 1996

Hartmann's solution is often regarded as the anaesthetic-panacea of fluid resuscitation. This crystalloid formulation is routinely employed as the rehydration and maintenance solution of choice in the operating theatre. In discussion with colleagues it became apparent that knowledge regarding the concentration of the constituent ions and the metabolism of the lactate content varied widely. We therefore decided to assess the level of knowledge about Hartmann's solution amongst the wider anaesthetic community.

Methods

We obtained permission from The Royal College of Anaesthetists to survey candidates attending the Part III FRCA College course in February 1996. At the end of an afternoon lecture session, those present were asked to complete a voluntary and confidential questionnaire. The candidates were given no time limit for completing the task, but were instructed not to confer with each other, nor to refer to texts. The questionnaire (see Appendix 1) asked for the following information:

1 the constituents and their concentrations in 1 litre of 0.9% sodium chloride;
2 the constituents and their concentrations in 1 litre of Hartmann's solution;
3 the purpose of the lactate in Hartmann's solution;
4 the metabolism of the lactate in Hartmann's solution.

In addition to the survey, we also reviewed the anaesthetic textbooks present in the anaesthetic library of The Royal London Hospital to establish the availability of 'source information' under the following headings:

1 Hartmann's solution – constituents, metabolism;
2 Ringer's lactate solution – constituents, metabolism;
3 lactate metabolism.

Results

All 82 candidates present in the lecture theatre completed a questionnaire. The median duration after qualification as a doctor was 6 years (range; 3.5–17 years). Time spent in anaesthetic practice was a median of 3.5 years (range; 2–15 years).

Question 1

All 82 (100%) knew that both sodium and chloride ions were present in 0.9% sodium chloride solution. The correct concentration of sodium was known by 30

Table 1 0.9% Sodium chloride.

Ionic constituent	British Pharmacopoeia (millimolar content)	Sodium chloride: percentage correct responses	
		Ion present	Millimolar content
Sodium ions	150 millimoles	100	37
Chloride ions	150 millimoles	100	35

Table 2 Hartmann's solution.

Ionic constituent	British Pharmacopoeia (millimolar content)	Hartmann's solution: percentage correct responses	
		Ion present	Millimolar content
Sodium ions	131 millimoles	100	34
Chloride ions	111 millimoles	95	60
Potassium ions	5 millimoles	96	46
Calcium ions	2 millimoles	78	17
Lactate ions	29 millimoles	91	15

(37%) and 29 (35%) correctly stated the chloride concentration (Table 1).

Question 2

When asked about the contents of Hartmann's solution, only the sodium ion was recognised as a constituent by all 82 (100%) of the candidates. Of these, 28 (34%) knew the correct concentration of this ion in solution (Table 2). Of the other four components of Hartmann's solution, none was identified as being present by *all* of the respondents. In particular, the presence of lactate ions was correctly suggested by 75 (91%) of respondents, but its millimolar concentration was only known by 12 (15%) (Table 2). In addition to the five component ions actually in Hartmann's solution, a further five components were suggested (Table 3). Only three (4%) of the 82 candidates knew the correct millimolar composition of Hartmann's solution, and only one stated the correct millimolar composition of both 0.9% sodium chloride *and* Hartmann's solution.

Question 3

In answering question 3, 52 (63%) of the participants suggested that lactate was metabolised to bicarbonate. A further 17 (21%) believed that glucose was also produced. In addition, five (6%) of those questioned suggested the presence of lactate was in order to produce a more 'physiological' solution.

Other suggestions for lactate included:

1 to act as a buffer;
2 as a pathway for free fatty acid production;
3 to maintain the Hartmann's solution as an isotonic preparation;

Table 3 Additional suggestions for constituents of Hartmann's solution.

Constituent	% of candidates making suggestion
Magnesium ions	7
Phosphate ions	2
Zinc ions	1
Bicarbonate	5
Dehydrogenase	1

4 to maintain the pH of the Hartmann's solution at 7.00;
5 to treat acidosis.

Question 4

Question 4 asked for a description of the metabolism of the lactate. The answers to this question were extremely varied, incomplete and imprecise. None of the replies correctly described lactate metabolism in its entirety. An incomplete but correct statement was made by 25 (31%) of respondents. Incorrect statements were made by 33 (42%) of respondents. No explanation was offered by 24 (29%) of the respondents.

We endeavoured to find a description of the metabolism of lactate from Hartmann's solution, in a number of standard anaesthetic texts (Appendix 2). Of the 11 textbooks reviewed only three offered any information regarding lactate metabolism. Scurr & Feldman (b) make brief reference to the formation of ATP from lactate following exercise and the generation of glycogen. Atkinson, Rushman & Lee (j) state that Hartmann's is a more

physiological solution and again very briefly describe the production of bicarbonate ions from lactate in the liver. They then go on to state that the bicarbonate thus generated counteracts any acidosis present.

The most information was contained in Yentis, Hirsch & Smith (k). They correctly state the millimolar concentrations of the constituent ions and then describe the two end-products of lactate metabolism. Firstly, they describe the slow production of bicarbonate ions in the liver over a few hours and also briefly describe the main route of metabolism in the liver, producing glucose, again using lactate as the substrate. A cautionary note is also made to exercise care when administering Hartmann's solution to patients suffering from diabetes mellitus.

Discussion

Sydney Ringer was born in 1834 and when in his mid-twenties trained at University College Hospital in London, becoming a full physician in 1866 [1]. He had both a busy and a varied medical career, in addition to developing as one of the earliest clinical research pharmacologists. One of his major areas of research concerned the effects of inorganic salts on body tissues, in particular cardiac muscle [2, 3].

As a result of his experimentation, he developed Ringer's solution. The constituent electrolytes of this solution were shown to be essential for tissue function. Indeed the solution could be used as a 'blood substitute' in which small organisms or tissue samples could function normally for short periods. The importance of his findings were not recognised for many years. However, Alexis Hartmann was to benefit from this work at a later date, adapting the solution that Ringer had developed for use in the clinical environment.

In 1898 Alexis Frank Hartmann was born in St Louis, Missouri. The family origins were Germanic, having later emigrated to North America. Hartmann studied at the Washington University School of Medicine in St Louis, gaining his MD in 1921. As a clinician his interest was in paediatrics. Like Ringer before him, he too pursued a scientific research career [1]. His research work centred around treating acidosis in sick children. At this time there were several problems complicating the use of sodium bicarbonate to achieve this end. Firstly, the process of sterilisation was laborious and, secondly, the highly irritant nature of the solution made administration difficult. Moreover the effect of sodium bicarbonate treatment often produced too rapid correction of the acidosis and indeed could produce a profound alkalosis. An alternative to sodium bicarbonate was needed [4].

Hartmann sought an isotonic solution that would produce a more moderate alkalinising effect, whilst retaining an electrolyte composition bearing more resemblance to plasma. This required the presence of proportionately less chloride than sodium in the replacement solution than was found in the 'normal' saline fashionable at the time.

Table 4 British Pharmacopoeia formulations for normal saline and Hartmann's.

Normal saline (Sodium chloride 0.9%)	Sodium	150 mmol.l^{-1}
	Chloride	150 mmol.l^{-1}
Hartmann's solution	Sodium	131 mmol.l^{-1}
	Potassium	5 mmol.l^{-1}
	Calcium	2 mmol.l^{-1}
	Chloride	111 mmol.l^{-1}
	Lactate	29 mmol.l^{-1}

From Ringer's work he found the ionic composition necessary to confer the electrolyte profile and added lactate to this formulation. Like Ringer before him he performed many experiments to confirm his findings. Finally he used the 'Lactated Ringer's Solution' clinically and confirmed its benefits and limitations in treating children with acidosis of various aetiologies.

Table 4 shows the British Pharmacopoeia formulations for Normal saline and Hartmann's solution. Any licensed manufacturer producing these solutions should have the concentrations of constituent ions as shown in Table 4 in their products and state them as such on the accompanying data sheet. However a range of concentrations within 95–105% of the stated ideal is considered acceptable.

The lactate in Hartmann's solution is metabolised by two routes, either gluconeogenesis or oxidation. About 70% of the lactate undergoes gluconeogeneis, predominantly in the liver and to a lesser extent in the kidneys. Both of these organs also oxidise lactate, a function which may also occur in cardiac and skeletal muscle under certain physiological conditions [5].

Lactate metabolism by gluconeogenesis is governed by the following overall equation:

$$2\underset{\text{lactate}}{CH_3CHOH\,COO^-} + 2H^+ \rightarrow \underset{\text{glucose}}{C_6H_{12}O_6}\ \text{(gluconeogenesis)}. \quad (1)$$

The lactate is first converted to pyruvate, then routed via oxaloacetate because the forward step governed by pyruvate kinase is irreversible, as are several other steps in the process (Fig. 1) as indicated by the unidirectional arrows. In normal healthy adults a transient increase in blood glucose is registered [4], provoking an appropriate insulin response.

Metabolism by oxidation of the lactate (about 30%) is

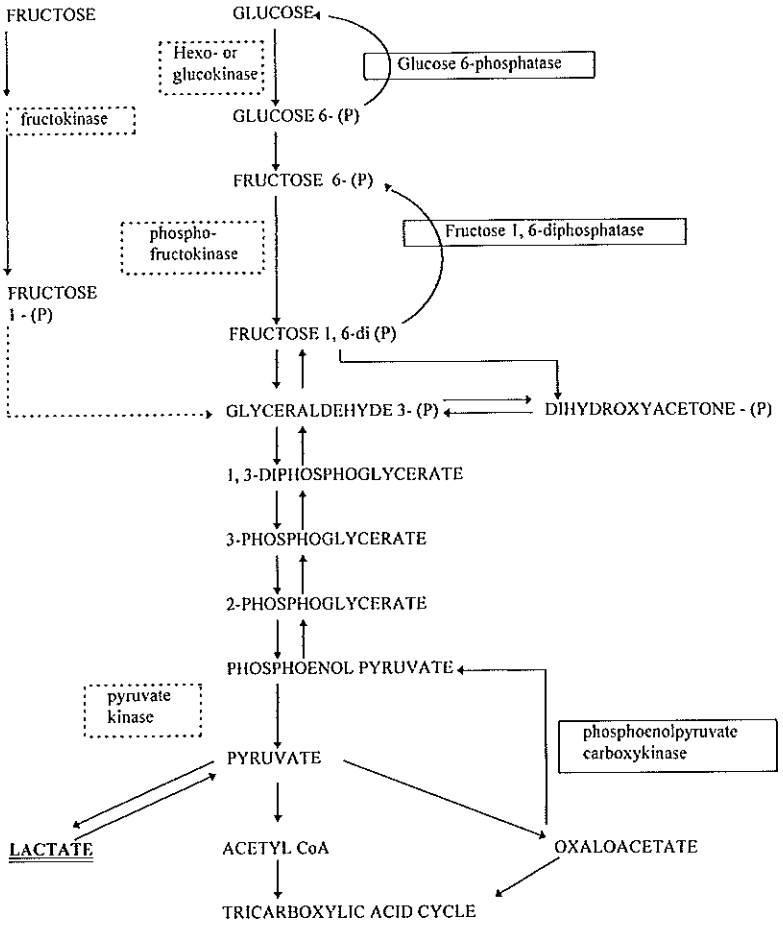

Figure 1 Metabolism of lactate.

governed by the next equation:

$$CH_3CHOH\,COO^- + H^+ + 3O_2 \rightarrow 3CO_2 + 3H_2O \text{ (oxidation)}. \quad (2)$$

The administered lactate is taken up by many cells, again predominantly the hepatocytes, where, during oxidation to CO_2 and H_2O, H^+ is consumed. It can be seen from the following two equations (Figs 2 and 3) that H^+ ions are

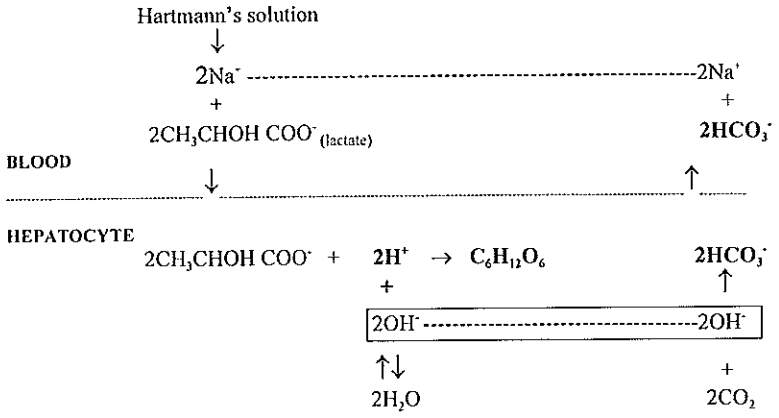

Figure 2 Metabolism of lactate to form glucose.

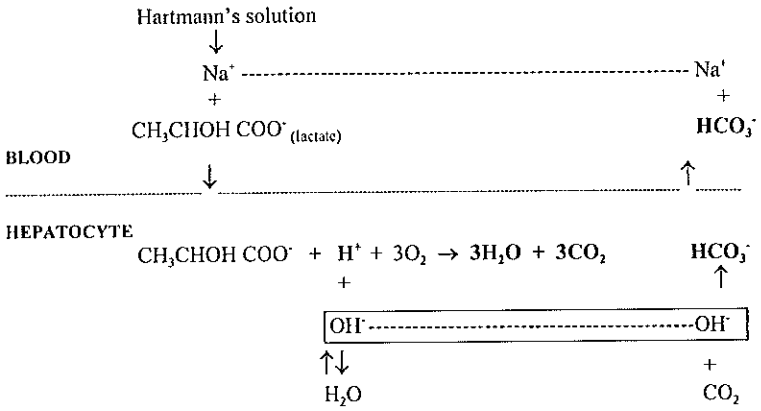

Figure 3 Metabolism of lactate by oxidation.

consumed in both gluconeogenesis and oxidation. Therefore both reactions contribute to the alkalinising effect by producing a relative excess of bicarbonate ions.

The consumption of H^+ leaves an excess of OH^- which is free to combine with CO_2 to form HCO_3^-. The production of bicarbonate from lactate has a half-life of 10–15 min and therefore takes about 1 h to be completed. Thus a steady stream of alkalinising agent is generated, reducing acidosis in a controlled fashion. If there is no acidosis to correct then the bicarbonate is usually excreted promptly by the kidneys and the mild alkalosis is transient [4]. However some critically ill patients are obligate excretors of acidic urine and the additional bicarbonate load generated from the lactate cannot be excreted, rendering the patient alkalotic and enhancing renal potassium loss [5].

In summary, the electrolyte composition of Hartmann's solution is similar to that first formulated by Sydney Ringer to maintain cellular function. Hartmann's solution has been adapted to resemble more closely the ionic composition of those simple ions in plasma, creating a 'balanced salt solution' that reduces transmembrane ion and water shifts post-transfusion. Alexis Hartmann largely achieved this change by adding sodium lactate. Hartmann's solution acts as a source of both glucose and alkalinising agent in the form of bicarbonate that is generated from lactate metabolism. For normal adults the production of both glucose and bicarbonate is gradual and produces small changes in their plasma concentrations, easily corrected by the usual homeostatic mechanisms. When fluid resuscitation is required in the face of metabolic acidosis, then the slow and steady production of bicarbonate is of potential benefit [6], but will occur even more slowly in shocked patients. Care should therefore be taken in monitoring the effects of infusion, when pathological conditions exist affecting lactate metabolism and the renal excretion of bicarbonate.

Our investigations reveal that there is little understanding of the reasons for including lactate in Hartmann's solution and even less of its metabolism. Standard textbooks are inadequate on the topic, although our review of all available texts was far from comprehensive. In anaesthetic practice, for the majority of patients, Hartmann's is the solution, but there are contra-indications to its use and these should be borne in mind.

Acknowledgments

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Appendix 1

This questionnaire is confidential and anonymous: it has no connection with the Royal College course or examinations

Completion is voluntary but your co-operation is appreciated, please do not confer

The summary results of this questionnaire may be used as part of a presentation, no individual replies will be quoted

How many years have you been qualified?

_____

How many years have you been giving anaesthetics?

_____

What is the precise electrolyte composition of 1 litre of
A. 0.9% NaCl?

_____

_____

_____

_____

B. Hartmann's solution _____

_____

_____

_____

_____

_____

_____

What is the purpose of the lactate in Hartmann's solution?

_____

_____

_____

Describe in as much detail as possible the metabolism of the lactate in Hartmann's solution (use a diagram if necessary)

_____

_____

_____

_____

Appendix 2

(a) *Anaesthesia*, 2nd edn. Smith & Aitkenhead (Churchill Livingstone) 1993.
(b) *Anaesthesia*, 4th edn. Scurr & Feldman (Heinemann Medical Books/Yearbook Medical Publishers) 1990.
(c) *Anaesthesia*, 4th edn. Ronald D. Miller (Churchill Livingstone) 1994.
(d) *Review of Medical Physiology*. William F. Ganong (Appleton and Lange) 1987.
(e) *Pharmacology and Physiology in Anaesthetic Practice*. Robert K. Stoelting (J. B. Lippincott Company) 1987.
(f) *General Anaesthesia*, 4th edn. Gray, Nunn & Utting (Butterworths) 1980.
(g) *General Anaesthesia*, 5th edn. Nunn, Utting & Brown (Butterworths) 1989.
(h) *Anaesthesia (1989)*. Nimmo & Smith (Blackwell Scientific Publications) 1989.
(i) *Anaesthesiology Review*; 2nd edn. Faust (Churchill Livingstone) 1994.
(j) *A Synopsis of Anaesthesia*, 11th edn. Atkinson, Rushman & Lee (Butterworth Heinmann) 1993.
(k) *Anaesthesia A to Z*. Yentis, Hirsch & Smith (Butterworth Heinemann) 1993.