140 mmol/L of sodium versus 77 mmol/L of sodium in maintenance intravenous fluid therapy for children in hospital (PIMS): a randomised controlled double-blind trial

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Summary

Background Use of hypotonic intravenous fluid to maintain hydration in children in hospital has been associated with hyponatraemia, leading to neurological morbidity and mortality. We aimed to assess whether use of fluid solutions with a higher sodium concentration reduced the risk of hyponatraemia compared with use of hypotonic solutions.

Methods We did a randomised controlled double-blind trial of children admitted to The Royal Children’s Hospital (Melbourne, VIC, Australia) who needed intravenous maintenance hydration for 6 h or longer. With an online randomisation system that used unequal block sizes, we randomly assigned patients (1:1) to receive either isotonic intravenous fluid containing 140 mmol/L of sodium (Na140) or hypotonic fluid containing 77 mmol/L of sodium (Na77) for 72 h or until their intravenous fluid rate decreased to lower than 50% of the standard maintenance rate. We stratified assignment by baseline sodium concentrations. Study investigators, treating clinicians, nurses, and patients were masked to treatment assignment. The primary outcome was occurrence of hyponatraemia (serum sodium concentration <135 mmol/L with a decrease of at least 3 mmol/L from baseline) during the treatment period, analysed by intention to treat. The trial was registered with the Australian New Zealand Clinical Trials Registry, number ACTRN1260900924257.

Findings Between Feb 2, 2010, and Jan 29, 2013, we randomly assigned 690 patients. Of these patients, primary outcome data were available for 319 who received Na140 and 322 who received Na77. Fewer patients given Na140 than those given Na77 developed hyponatraemia (12 patients [4%] vs 35 [11%]; odds ratio [OR] 0·31, 95% CI 0·16–0·61; p=0·001). No clinically apparent cerebral oedema occurred in either group. Eight patients in the Na140 group (two potentially related to intravenous fluid) and four in the Na77 group (none related to intravenous fluid) developed serious adverse events during the treatment period. One patient in the Na140 had seizures during the treatment period compared with seven who received Na77.

Interpretation Use of isotonic intravenous fluid with a sodium concentration of 140 mmol/L had a lower risk of hyponatraemia without an increase in adverse effects than did fluid containing 77 mmol/L of sodium. An isotonic fluid should be used as intravenous fluid for maintenance hydration in children.

Introduction

The appropriate sodium concentration of intravenous fluid used to maintain hydration in children in hospital has generated much debate.2–4 Traditionally, these fluids have contained sodium concentrations as low as 30 mmol/L—much less than the sodium concentration in plasma. The use of such hypotonic fluid in children has been reported to be a cause of hyponatraemia, with some children having severe outcomes such as seizures, cerebral oedema, and death.2–4 Antidiuretic hormone contributes to the development of hyponatraemia through reduction in excretion of water, reducing the body’s capacity to compensate for increased water loads. Common indications for children to be admitted into hospital, including febrile and infectious illnesses and surgical procedures,5–9 have been associated with increased antidiuretic hormone concentrations, suggesting that more children are at risk of hyponatraemia and associated complications than were previously thought.

Recognition of the association between hyponatraemia and intravenous fluid has increased and some authorities have recommended use of the sodium concentration of 75 mmol/L in maintenance fluid therapy, much higher than was previously used8 but cases of hyponatraemia continue to be noted.10 Randomised trials of intravenous fluid in specific subpopulations, particularly those involving postoperative and intensive care patients, have suggested that use of an isotonic fluid with a similar sodium concentration to plasma might reduce risk of hyponatraemia.10–12 However, evidence from large heterogeneous populations of children in hospital is scarce.13 Additionally, some investigators have raised concerns about potential adverse outcomes from widespread use of isotonic intravenous fluids, including hyponatraemia,13,14 fluid overload,15 and hyperchloremic acidosis.13,16

In the Paediatric Intravenous Maintenance Solution (PIMS) study, we did a randomised controlled trial in a heterogeneous population of children admitted to...
one hospital to establish whether an isotonic fluid (140 mmol/L of sodium [Na140]) reduced the risk of hyponatraemia compared with a hypotonic fluid (77 mmol/L of sodium [Na77]) without an increase in adverse effects.

Methods

Study design and patients

We did a randomised, double-blind trial at The Royal Children’s Hospital, Melbourne, VIC, Australia, a tertiary paediatric teaching hospital and specialist referral centre. Eligible participants were children aged between 3 months and 18 years that needed intravenous maintenance fluid. We chose 3 months as the lower age limit because infants younger than this age might be at greater risk of hypernatraemia because of their reduced renal concentrating ability, and might need more than 5% glucose. We defined maintenance fluid volumes as between 50% and 150% of the daily volumes recommended by Holliday and Segar.11 We excluded children who met any of the following criteria: an initial plasma sodium concentration of lower than 130 mmol/L or higher than 150 mmol/L; diabetes insipidus or diabetic ketoacidosis; renal disease that needs dialysis; a disorder causing excessive renal sodium excretion (eg, Addison’s disease, congenital adrenal hyperplasia, or Bartter’s syndrome); preoperative or postoperative neurosurgical patients; those who had undergone craniofacial surgery that needed the cranial cavity to be opened; protocol-determined chemotherapy hydration; meningitis proven by either turbid cerebrospinal fluid or microscopy of cerebrospinal fluid; severe liver disease; inborn errors of metabolism that needed protocol-determined fluid therapy; and disorders in which intravenous fluids were expected to be given for shorter duration than 6 h. We recruited most patients in the hospital’s emergency department and presurgical wards, with the treating team identifying most potential participants. A researcher obtained written informed consent from the parents or guardian of all children and, when appropriate, directly from adolescent participants. The study was approved by The Royal Children’s Hospital Human Research Ethics Committee and was overseen by an independent data monitoring committee (DSMC) reviewed interim safety and efficacy data at planned 6 monthly intervals.

Randomisation and masking

We randomly assigned patients (1:1) to either Na140 or Na77 using an online randomisation system. Randomisation was stratified by baseline serum sodium concentrations (low <135 mmol/L, normal 135–145 mmol/L, high >145 mmol/L). The randomisation schedule was computer generated by an independent statistician using block randomisation with unequal block sizes.

Study investigators, treating clinicians, nurses, and patients were masked to assigned fluid type throughout the study. Fluid type was blinded under the supervision of an independent pharmacist. Fluids were concealed in sealed opaque bags which were identical in appearance. The fluid bags were kept in eight groups (A to H); four groups contained Plasma-lyte148 with 5% glucose, containing 140 mmol/L of sodium (Na140), and four groups contained 0.45% sodium chloride with 5% glucose, containing 77 mmol/L of sodium (Na77; table 1). We used this method because individual study numbers on blinded bags was logistically impractical and because participants would need different quantities of fluid bags, depending on their weight, fluid rate prescribed, and length of treatment. Eight groups (labelled with letters A to H) were used, rather than two, to ensure that blinding was maintained.

Procedures

Potentially eligible patients had a serum sodium measurement taken no more than 4 h before allocation. When a patient had a surgical procedure before the start of intravenous maintenance fluid, the serum sodium was taken at the end of the procedure. This result was entered into the online randomisation program, which then provided the patient’s study number and treatment allocation, corresponding to a blinded bag of fluid. Patients started study fluid at a rate decided by the treating physician. Study fluid was continued for 72 h or until the patient was receiving less than 50% of standard maintenance rate (defined as the treatment period), at which time they were changed to an intravenous fluid of the treating clinician’s choice, if needed. Study fluid was stopped earlier when the sodium decreased to lower than 130 mmol/L or increased to higher than 150 mmol/L with a change of at least 3 mmol/L compared with baseline, the patient withdrew consent, or when the treating clinician decided that continuing with the study fluid was no longer in the child’s best interest. When patients stopped receiving study fluid early they continued to be monitored and outcome data were collected when possible.

<table>
<thead>
<tr>
<th>Na⁺ (mmol/L)</th>
<th>Cl⁻ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Mg²⁺ (mmol/L)</th>
<th>Acetate (mmol/L)</th>
<th>Gluconate (mmol/L)</th>
<th>Glucose (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-lyte148 solution with 5% glucose (140 mmol/L sodium; isotonic)</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>1.5</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>0.45% sodium chloride with 5% glucose (77 mmol/L sodium; hypotonic)</td>
<td>77</td>
<td>77</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The treating clinician could add potassium chloride to the study fluids when clinically indicated. Because the clinician was masked to the fluid allocation, they were made aware that the fluid could contain 5 mmol/L more potassium than ordered in patients allocated to 140 mmol/L sodium.

| Table 1: Composition of study fluids |
We measured serum electrolytes (concentrations of sodium, potassium, chloride, bicarbonate, urea, creatinine, and glucose) after 6, 24, 48, and 72 h of treatment, until the study fluid was stopped. We also recorded and used for analysis the results of any additional blood tests requested by the treating clinician. Blood electrolyte concentrations were measured by a direct ion selective sensor using a RapidLab 1265 Blood Gas Analyser (Siemens, Munich, Germany) or an VITROS 5600 Integrated System (Ortho-Clinical Diagnostics, Rochester, NY, USA). We measured urinary electrolytes about 24 h after each patient started treatment.

The treating team monitored all patients for clinical signs of overhydration. Nursing or medical staff did a standardised hydration assessment when the patient was clinically assessed as dehydrated or overhydrated and on all patients when the study fluid was stopped (appendix). Members of the study team examined the patient’s clinical records daily for references to hydration status.

We prospectively collected information about serious adverse events, defined as unexpected intensive care admissions or unexpected life-threatening deteriorations in health. The independent data and safety monitoring committee (DSMC) reviewed interim safety and efficacy data at planned 6 monthly intervals.

Outcomes

The primary endpoint was occurrence of hyponatraemia during the treatment period (within 72 h of the start of study fluid or until the patient was receiving less than 50% of standard maintenance rate). Hyponatraemia was defined as a serum sodium measurement below the normal range minimum (<135 mmol/L), with a decrease of at least 3 mmol/L compared with the baseline measurement. The baseline measurement was the last result before the start of study fluid. A 3 mmol/L decrease was included to account for patients who were already hyponatraemic at enrolment and to allow for laboratory measurement error.

Secondary outcomes were the occurrence of hypernatraemia (>145 mmol/L, with an increase of at least 3 mmol/L compared with baseline); severe hyponatraemia (<130 mmol/L, with at least 3 mmol/L decrease); severe hypernatraemia (>150 mmol/L, with at least 3 mmol/L increase); hyperchloreaemia (>110 mmol/L); high serum magnesium (>1·2 mmol/L), and high serum bicarbonate (>30 mmol/L) during the treatment period; and the mean serum sodium and mean change in weight at 6, 24, 48, and 72 h after the start of study fluid. Other secondary outcomes were overhydration and dehydration, the need for intravenous cannula reinsertion, seizures, or clinically apparent cerebral oedema during the treatment period.

Statistical analysis

The sample size calculation was based on a reduction in the proportion of participants with hyponatraemia from 10% in the Na77 group (a rate of hyponatraemia based on previous work24 and an unpublished internal audit) to 4% in the Na140 group. We believed that a reduction to 4% was realistic and of a sufficient magnitude to be clinically significant. To power the study to identify a reduction from 10% to 4%, we needed 320 patients in each treatment group (based on 80% power and a two-sided test with α=0·05). An additional 25 patients in each treatment group (8%) were recruited to allow for participants for whom no primary outcome data were available, bringing the total sample size to 690.

For the primary endpoint, we did an intention-to-treat analysis by including all randomly assigned participants who met the inclusion criteria at the time of starting fluids and had at least one serum sodium test taken during the treatment period. Because most (641 [95%] of 676) eligible and randomly assigned participants in each treatment group (8%) were recruited to allow for participants for whom no primary outcome data were available, bringing the total sample size to 690.

For the primary endpoint, we did an intention-to-treat analysis by including all randomly assigned participants who met the inclusion criteria at the time of starting fluids and had at least one serum sodium test taken during the treatment period. Because most (641 [95%] of 676) eligible and randomly assigned participants had at least one sodium measurement taken during the study period, we did a complete case analysis as the primary analysis. Similarly, we analysed all other outcomes using the intention-to-treat principle when outcome data were available. As a sensitivity analysis, we did multiple imputation to assess the effect of missing data on the analysis of all primary and secondary outcomes.
We made comparisons between the groups using logistic regression for binary outcomes and linear regression for continuous outcomes. Results are presented as differences between proportions and odds ratios (ORs) for binary outcomes and mean differences for continuous outcomes, adjusted for baseline sodium as a continuous measure (only 1% of patients had a high baseline sodium).

As a preplanned sensitivity analysis, we also compared the primary outcome between the groups once adjusted for the following potential confounding variables: preplanned intensive care unit admission at time of randomisation; surgery done either immediately before randomisation or during the treatment period (since the composition of intravenous fluid was not thought to affect a participant’s need for surgery); and age at recruitment (as a continuous variable). Further sensitivity analyses adjusted for total fluid volume received, excluded participants receiving drugs known to affect sodium concentrations, and included only sodium measurements taken at the specified times (6, 24, 48, and 72 h) to avoid potential bias due to more blood tests in one treatment group. We did a preplanned sensitivity analysis to remove samples that were potentially affected by contamination with study fluid (appendix). We did a preplanned subgroup analysis to compare the primary outcome between patients randomly assigned to Na140 and Na77 according to age categories of younger than 1 year, 1–5 years, 5–12 years, and 12 years and older; and according to whether participants did or did not undergo a surgical procedure during or immediately before the treatment period, have a low serum sodium at baseline, or have a preplanned admission to an intensive care unit at the time of randomisation.

All analyses were done with Stata version 12. The study protocol was registered with the Australia New Zealand Clinical Trial Registry, number ACTRN12609000924257.

Role of the funding source
The funders of this study had no role in study design or collection, analysis, or interpretation of the data. They were not involved in writing the study report, nor the decision to submit this report for publication. All authors had access to all the data, all authors have final responsibility for the decision to submit for publication.

Results
Between Feb 2, 2010, to Jan 29, 2013, 1109 children needing intravenous maintenance fluid were referred to the study team (figure 1). Of the 690 children randomly assigned, 13 were randomised in error and one withdrew consent for any data to be used, resulting in 676 patients available for analysis (338 in each treatment group). These patients were used in all analyses when possible. However, 35 patients (5%) did not have a blood test done after starting study fluid, resulting in missing data for most outcomes, including the primary endpoint. Our primary analysis is based on the remaining 641 participants, 319 in the Na140 group and 322 in the Na77 group. The 35 children without primary outcome data were similar to children with primary outcome data for all baseline and treatment characteristics except for age (19 [54%] without primary outcome data were younger than 5 years vs 210 [33%] with primary outcome data), mean weight (22 kg [SD 15] vs 33 kg [21]), and median treatment duration (5 h [IQR 3–14] vs 23 h [16–30]). Baseline characteristics were similar between the treatment groups, apart from more infants younger than 1 year being allocated to the Na140 group (table 2). Participants had a broad range of diagnoses (appendix). Almost half of the patients underwent an operation immediately before or during the treatment period, with similar numbers of elective and emergency surgeries.

<table>
<thead>
<tr>
<th>Sodium (mmol/L)</th>
<th>Na140 (n=338)</th>
<th>Na77 (n=338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>137 (3)</td>
<td>138 (3)</td>
</tr>
<tr>
<td>Range</td>
<td>131–148</td>
<td>131–147</td>
</tr>
</tbody>
</table>

Data are mean (SD), n (%), or range. Na140=fluid with 140 mmol/L of sodium. Na77=fluid with 77 mmol/L of sodium. *n=467; 241 in Na140 group, 226 in Na77 group. Weights that were measured more than 10 min after the start of study fluid were excluded from analysis.

Table 2: Baseline characteristics

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Na140 (n=338)</th>
<th>Na77 (n=338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underwent surgical procedure</td>
<td>148 (44%)</td>
<td>164 (49%)</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>67 (20%)</td>
<td>92 (27%)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>81 (24%)</td>
<td>72 (21%)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>9 (3%)</td>
<td>13 (4%)</td>
</tr>
<tr>
<td>Volume of study fluid received (mL)*</td>
<td>1073 (698–2158)</td>
<td>1240 (725–2434)</td>
</tr>
<tr>
<td>Volume of study fluid received as a percentage of standard maintenance volume</td>
<td>80% (66–91%)</td>
<td>80% (67–92%)</td>
</tr>
<tr>
<td>Volume of oral fluid received (mL)</td>
<td>370 (100–700)</td>
<td>300 (60–600)</td>
</tr>
<tr>
<td>Treatment period (h)</td>
<td>21 (15.3–45.0)</td>
<td>22.3 (15.4–45.8)</td>
</tr>
</tbody>
</table>

Data are n (%) or median (IQR). Na140=fluid with 140 mmol/L of sodium. Na77=fluid with 77 mmol/L of sodium. *n=467; 241 in Na140 group, 226 in Na77 group. Weights that were measured more than 10 min after the start of study fluid were excluded from analysis.

Table 3: Treatment period characteristics
The volume of study fluid received and length of treatment periods were also similar between groups (table 3). Fewer participants allocated to Na140 developed hyponatraemia than did those allocated to Na77 (12% vs 35%; OR 0·31, 95% CI 0·16–0·61; p=0·001; table 4). Seven patients developed severe hyponatraemia during the study, with little evidence of a difference between the two treatment groups (OR 0·35, 95% CI 0·07–1·8; p=0·21; table 4). Of note, no patients developed symptomatic hyponatraemia. Eight patients (four in each treatment group) were changed to an open-label, high-sodium-containing fluid by the treating clinician due to safety concerns after developing moderate hyponatraemia (130 mmol/L to <135 mmol/L). None of these children developed severe hyponatraemia. The occurrence of hypernatraemia was similar in the two groups: 14 (4%) participants developed hypernatraemia in the Na140 group, compared with 18 (6%) in the Na77 group (OR 0·80, 95% CI 0·39–1·65; p=0·55; table 4).

Our estimate for the difference in the primary endpoint between the two groups was similar in all prespecified sensitivity analyses, including the analysis adjusted for age in which there was a slight baseline imbalance (appendix). Of note, the median volume of study fluid given was similar for patients who did and did not reach the primary endpoint: patients becoming hyponatraemic received a median of 1169 mL (IQR 569–2920), whereas those who did not become hyponatraemic received 1180 mL (712–2303). Use of multiple imputation to account for the missing data did not change the

<table>
<thead>
<tr>
<th>Percentage or mean difference (95% CI)</th>
<th>Adjusted* odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatraemia</td>
<td>Na140 319 Na77 322</td>
<td>12 (3·8%) 35 (10·9%)</td>
</tr>
<tr>
<td>Severe hyponatraemia†</td>
<td>Na140 319 Na77 322</td>
<td>2 (0·6%) 5 (1·6%)</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Na140 319 Na77 322</td>
<td>14 (4·4%) 18 (5·6%)</td>
</tr>
<tr>
<td>Severe hyponatraemia§</td>
<td>Na140 319 Na77 322</td>
<td>1 (0·3%) 3 (0·9%)</td>
</tr>
<tr>
<td>Hyperchloraemia (&gt;110 mmol/L)</td>
<td>Na140 318 Na77 319</td>
<td>32 (12·3%) 51 (16·0%)</td>
</tr>
<tr>
<td>High serum bicarbonate (&gt;30 mmol/L)</td>
<td>Na140 314 Na77 318</td>
<td>6 (1·9%) 7 (2·2%)</td>
</tr>
<tr>
<td>High serum magnesium (&gt;1·2 mmol/L)</td>
<td>Na140 313 Na77 316</td>
<td>1 (0·3%) 0</td>
</tr>
<tr>
<td>Mean (SD) serum sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 h</td>
<td>Na140 287 Na77 296</td>
<td>138·6 (2·8) 138·5 (3·6)</td>
</tr>
<tr>
<td>At 24 h</td>
<td>Na140 145 Na77 163</td>
<td>139·9 (3·4) 139·7 (3·4)</td>
</tr>
<tr>
<td>At 48 h</td>
<td>Na140 64 Na77 67</td>
<td>139·8 (3·5) 139·0 (2·9)</td>
</tr>
<tr>
<td>At 72 h</td>
<td>Na140 25 Na77 29</td>
<td>140·3 (3·5) 139·3 (2·9)</td>
</tr>
<tr>
<td>Urinary sodium at 24 h</td>
<td>Na140 113 Na77 125</td>
<td>138·4 (80·3) 175·9 (45·8)</td>
</tr>
</tbody>
</table>

Table 4: Primary and secondary outcomes

Data are n, n (%), or mean (SD) unless otherwise stated. Na140=fluid with 140 mmol/L of sodium. Na77=fluid with 77 mmol/L of sodium. *Adjusted for baseline sodium.

Episodes of overhydration 18 (5%) 12 (4%) –3·8% (4·9 to 1·3) 0·47 (0·69–2·3) 0·32
Episodes of dehydration 26 (8%) 26 (8%) 0% (4·0 to 0·0) 0·96 (0·54–1·7) 0·89
Seizures 1 (0·3%) 7 (2%) 1·8% (0·2–3·4) 0·15 (0·02–1·2) 0·07
Cerebral oedema 0 0 0
Intravenous line reinsertion 3 (12%) 30 (9%) –2·7% (7·2 to 1·9) 1·34 (0·81–2·22) 0·25
Serious adverse events 8 (2%) 6 (1%) –1·2% (3·2 to 0·8) 1·96 (0·58–6·61) 0·28

Table 5: Adverse events

Data are n (number of patients with at least one event; %) unless otherwise specified. Na140=fluid with 140 mmol/L of sodium. Na77=fluid with 77 mmol/L of sodium. *Adjusted for baseline sodium.

Figure 2: Time to hyponatraemia
conclusions for the comparisons for the primary and secondary endpoints (appendix).

An analysis of the time to hyponatraemia provided strong evidence for a reduced risk of hyponatraemia with Na140 compared with Na77 (HR 0·34, 95% CI 0·18–0·66; p=0·003). The Kaplan-Meier curve (figure 2) suggests that the risk of hyponatraemia might be greatest in the first 6 h in both treatment groups; and that the Na140 group had a very small risk of hyponatraemia beyond the first day of treatment compared with a continuing risk for those in the Na77 group.

The prespecified subgroup analysis (appendix) showed similar evidence of reduced odds of hyponatraemia in the Na140 group in the various age groups and when separated by the baseline sodium concentration. A similar magnitude of effect was present in surgical (OR 0·32, 95% CI 0·12–0·82; p=0·02) and non-surgical patients (OR 0·32, 0·12–0·85; p=0·02). Similarly, there was evidence of reduced odds of hyponatraemia with Na140 compared with Na77 in both patients in intensive care (OR 0·15, 0·01–2·08; p=0·00) and patients not in intensive care (OR 0·34, 0·16–0·68; p=0·003). The difference in the proportions of patients with hyponatraemia in the two treatment groups in the 18 patients in intensive care was large (46%) of 11 patients allocated to Na77 vs 1 (14%) of seven patients allocated to Na140, but resulted in a wide confidence interval because of the small sample size. We did not include data for change in weight from baseline in the analysis, despite being a prespecified secondary outcome, because we only had reliable baseline data for 193 (29%) participants.

A similar proportion of patients had clinical overhydration and intravenous line reinsertion in the two treatment groups (table 5). One patient had one or more seizures in the Na140 group compared with seven who had them in the Na77 group; none of these participants met our primary endpoint and all had a known seizure disorder. One patient with seizures who was allocated to Na77 had a decrease in serum sodium higher than 0·5 mmol/L per h (6·0 mmol/L in 5 h). This patient had several clusters of seizures, with the first cluster documented after the decrease in serum sodium. Clinically apparent cerebral oedema did not occur in either treatment group.

Eight patients in the Na140 group and four in the Na77 group developed serious adverse events during the treatment period. Two patients receiving Na140 had episodes in which overhydration contributed to clinical deterioration; intravenous fluid was thought to be a potential contributor (appendix). No events in the Na77 group were thought to be related to study fluid.

Discussion

Our findings show that children given an isotonic fluid with 140 mmol/L of sodium had a lower risk of developing hyponatraemia than did those given fluid containing 77 mmol/L of sodium. Despite previous concerns for isotonic maintenance solutions, we noted no evidence for a difference in the proportion of patients with hypernatraemia between the two treatment groups. The rate and type of adverse outcomes, including overhydration and intravenous line reinsertion, were also similar between groups. We noted little evidence of an increase in serious adverse events with Na140; however, these serious events were rare in this study and monitoring is needed.

After the landmark paper by Holliday and Segar, fluids with between 30 mmol/L and 50 mmol/L of sodium were routinely prescribed for children who needed maintenance intravenous fluid. Several decades after Holliday and Segar’s article, the identification of adverse effects related to hyponatraemia, including permanent neurological deficit and death, resulted in some countries, and our hospital, recommending a change to increase the sodium concentration of intravenous fluid to at least 75 mmol/L. The results of our study suggest that hyponatraemia will occur in about 11% of children receiving such a fluid. We have shown that, by using a fluid with a similar sodium concentration to plasma, the risk of hyponatraemia can be reduced, with little evidence of an increase in adverse events.

Although previous reports have recommended the use of an isotonic fluid in some children, particularly critically ill children and those needing surgery (panel), our study was done in a broad population of children in hospital. Results of our additional analyses showed that the risk of hyponatraemia was reduced across all predefined subgroups and after we adjusted for fluid volume. Our study is the largest randomised controlled trial to compare isotonic maintenance fluid with hypotonic maintenance fluid. We recruited children with the widest possible range of diagnoses, making it directly relevant to hospital-wide guidelines for standard fluid maintenance therapy. Patients were followed up for up to 72 h, which is longer than in most studies comparing isotonic with hypotonic intravenous fluids, although not surprisingly, the number of patients in the study decreased with time—308 children had their serum sodium concentration measured at 24 h, 131 at 48 h, and 54 at 72 h, because participants no longer needed fluid. Importantly, participants and clinicians were masked to treatment allocation and the frequency of blood sampling was standardised across the two treatment groups.

Our study has some limitations. Primary outcome data were not recorded for 5% of randomly assigned and eligible participants, mostly due to a short duration of intravenous fluid administration or parental refusal of blood test. Although differences existed in the age and treatment duration of the participants with and without outcome data, multiple imputation for missing data did not change the conclusions, suggesting that the small amount of missing data is unlikely to have had an effect on our results. Infants younger than 3 months
were excluded from this study because of concerns that they might be at greater risk of hyponatraemia and that 5% glucose might be inadequate in children of this age. The appropriate maintenance intravenous fluid for neonates should be assessed in a separate study. The first serum sodium measurement was taken after 6 h of fluid therapy. Previously, evidence for when the sodium nadir might occur has been inadequate because the nadir is probably affected by interplay between severity of illness causing antiuretic hormone secretion and length of treatment. The Kaplan-Meier curve (figure 2) suggests that the risk of development of hyponatraemia might be greatest in the first 6 h. Importantly, hyponatraemia might have been missed in patients before the first sample was taken or in those receiving intravenous fluids for shorter periods than was required for entry into this study (expected minimum of 6 h). Our study included several secondary outcomes, hence caution should be applied in interpretation of the strength of the treatment effect for these secondary outcomes.

Arguably, hyponatraemia itself is not an important outcome. However, even mild hyponatraemia has been associated with adverse clinical outcomes in children and adults, including an increased risk of mortality, extended stays in intensive care units, and increased invasive and non-invasive ventilator support.45-48 Our study incorporated safety mechanisms, including the removal of any patients who developed severe hyponatraemia. The removal of patients who developed severe hyponatraemia meant that it was not possible to identify a difference in episodes of cerebral oedema between treatment groups because participants were removed before developing this disorder. Our primary outcome included a decrease in serum sodium of at least 3 mmol/L to account for measurement error and to ensure that, in patients recruited who were hyponatraemic at baseline, the primary endpoint corresponded to a deterioration in serum sodium.

Although our study suggests that isotonic fluid is preferable to hypotonic fluid, other considerations or further study are needed to establish which of the available isotonic fluids is preferable. We used a balanced solution (Plasma-lyte148 with 5% glucose). Other isotonic fluids might have different risk profiles due to differences in sodium load, the risk of drug and blood product incompatibilities, or higher chloride concentration (such as in 0·9% sodium chloride). Studies in adult patients have suggested that hyperchloremic acidosis, which can be induced by 0·9% sodium chloride, can be associated with adverse events including decreased gastric perfusion, renal impairment, and increased mortality.49-51 About 13% of patients in our study had concentrated potassium added to the study fluid, and an audit of fluid prescribing in a paediatric intensive care population reported that 31% of patients receiving Plasma-lyte148 had potassium added.44 The availability of concentrated potassium on a ward raises a substantial safety concern because of the risk of inadvertent administration. These issues need to be addressed with fluid manufacturers to ensure that maintenance fluids both with and without potassium are available for administration. This trial has shown that, in children who need maintenance fluid therapy, use of an isotonic fluid reduces the risk of hyponatraemia compared with use of a hypotonic fluid, with little evidence that this fluid increases the risk of adverse outcomes.

Contributors
SM searched the published work. SM, AD, TD, and KJL led the study design, with all authors contributing. SM and HT contributed to the data collection. KJL and SJA did the data analysis. All authors contributed to the data interpretation. SM wrote the first draft of the manuscript with all authors contributing to revisions.

Declaration of interests
We declare no competing interests.

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