The use of isotonic fluid as maintenance therapy prevents iatrogenic hyponatremia in pediatrics: A randomized, controlled open study*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Describe the incidence of both hyponatremia and hypernatremia and their relationship to the type of maintenance fluids used in the management of critically ill infants and children.
2. Identify the potential deleterious impact of the use of hypotonic maintenance fluids in the management of critically ill infants and children.
3. Appraise reexamination of current recommendations regarding maintenance fluid management in critically infants and children.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objectives: **Hypotonic fluids are widely used in pediatrics. Several articles have reported the risk of iatrogenic hyponatremia secondary to this practice. We primarily intend to determine whether the use of isotonic fluids prevents hyponatremia and, secondly, whether these fluids increase the incidence of adverse events.**

Study Design: **One hundred twenty-two pediatric patients hospitalized in intensive care unit requiring maintenance fluid therapy were randomized to receive isotonic fluids (isotonic group, NaCl = 140 mEq/L) or hypotonic fluids (hypotonic group, NaCl <100 mEq/L). Electrolyte blood concentration, glycaemia, and blood pressure were measured at 0, 6, and 24 hrs after the beginning of fluid therapy. Plasma creatinine, urine specific gravity, and urine electrolyte concentration were measured at 6 hrs. Standard intention-to-treat analysis and Bayesian analysis were conducted to assess the probability of hyponatremia and hypernatremia in each group.**

Results: **At the time of admission to hospital, no differences in natremia or the percentage of hyponatremia were found between groups. At 24 hrs, the percentage of hyponatremia in the hypotonic group was 20.6% as opposed to 5.1% in the isotonic group ($p = 0.02$). No differences in the number of adverse events other than hyponatremia were observed between groups.**

Conclusions: **The use of hypotonic fluids increases the risk of hyponatremia when compared with isotonic fluids at 24 hrs following infusion (number needed to harm [confidence interval 95%] = 7[4;25]). In our sample, the use of isotonic fluids did not increase the incidence of adverse events compared with hypotonic fluids. (Pediatr Crit Care Med 2008; 9:589–597)**

KEY WORDS: hyponatremia; hypotonic fluids; isotonic fluids; intravenous fluids

The optimum composition of intravenous fluid in pediatric patients remains a mystery to date. In 1956, Holliday and Segar (1) suggested that daily electrolyte requirements might be similar to oral requirements. Because lactating children achieved adequate growth and natremia levels when fed with mother's milk or an adapted formula—containing between 10 and 30 mEq sodium per liter—they assumed that this concentration would be suitable for administration as an intravenous solution. Although this hypothesis has not been confirmed in any clinical trial, hypotonic solutions with a sodium concentration lower than the concentration in plasma are used as common maintenance fluid therapy in pediatrics. This should not be associated with any risks in healthy children, but it may have undesired effects in ill children with a limited ability to excrete free water.

***See also p. 658.**

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Several nonosmotic stimuli for the secretion of antidiuretic hormone have been described, many of which are frequent among hospitalized patients, such as central nervous system infections (2), respiratory system and digestive system infections (3), postsurgical infections (4), opiate use, pain, and nausea (5). Therefore, it is common that hospitalized children requiring maintenance fluid therapy have a predisposition to retain free water. A fluid therapy based on hypotonic liquids implies the administration of large amounts of free water and, thus, this could induce iatrogenic hyponatremia and the subsequent risk of cerebral edema. In an observational study on hospitalized children, Hoorn et al. (6) found that the prolonged administration of hypotonic fluids was related to a decrease in natremia proportional to the amount of free water administered. Recently, many authors have associated the use of hypotonic solutions with a higher incidence of hyponatremia-related permanent encephalic lesions and death (7–10).

The administration of isotonic liquids as maintenance fluid therapy reduces antidiuretic hormone secretion (2, 11) and, in a randomized trial on postsurgical adult subjects, also the risk of iatrogenic hyponatremia (4). Hence, several authors currently recommend the use of isotonic fluids as a maintenance therapy for pediatric patients (5, 12, 13). However, clinical practice guidelines continue to use the recommendations published 50 years ago (14) in view of the theoretical risks supposed to this type of solutions—hypernatremia, hypertension because of volemic increase and phlebitis because of supraphysiological osmolarity (15). To date, no side effects have been reported with the use of isotonic solutions as maintenance therapy in pediatrics.

We designed this randomized, open, controlled study to assess the differences between the incidence of hyponatremia and plasma sodium variations during maintenance fluid therapy infusion with hypotonic and isotonic fluids in hospitalized children in a pediatric intensive care unit. In addition, we also evaluated the incidence of side effects that could theoretically condition the use of isotonic fluids: hypernatremia, phlebitis, and hypertension.

PATIENTS AND METHODS

Protocol. This is a prospective, controlled, randomized with blind and open phases conducted at the pediatric intensive care unit at the Hospital Infantil La Fe in Valencia (Spain) between January and March 2006. Children ages between 29 days and 18 years requiring hospitalization at our service could be included in the randomization of the study only when their physician prescribed intravenous maintenance fluid therapy. Patients with chronic or acute kidney failure, at risk of cerebral edema (diabetic ketoacidosis or craneoencephalic trauma), with plasma sodium levels at hospital admission <130 mEq/L or >150 mEq/L, and/or dehydration >5% of the patient's body weight were excluded from the study.

The subjects' parents or guardians were informed of the study protocol and its risks, and if they gave their consent, the children were randomized into two groups: the hypotonic group (control) receiving maintenance fluids with sodium concentrations between 20 and 100 mEq/L (corresponding to 2–4 mEq/Kg/24 hr) and the isotonic group (experimental) receiving fluids with a sodium concentration of 140 mEq/L and potassium concentration of 15 mEq/L (tonicity = 155 mOsm/L). In both groups, the daily total volume of liquid infused was determined by the volumetric Holliday–Segar (1) formula. The remaining ionic and glucose concentrations in the drip of the two groups were the same (5% dextrose). When required, oral tolerance was begun and intravenous fluid was interrupted following the same criteria in both groups, i.e., the ones commonly used at our service.

Because of safety reasons, several withdrawal criteria after inclusion in this study were also established: a plasma sodium measurement <130 mEq/L or >150 mEq/L, acquired abnormalities involving sodium or free water kidney excretion (inadequate antidiuretic hormone secretion or diabetes insipidus), or the interruption of fluid therapy by order of the physician.

The main dependent study end point is the percentage of hyponatremia acquired during treatment with fluid therapy. To determine hyponatremia, ion blood concentrations were calculated for each patient at the time of hospital admission at 6 hrs and at 24 hrs. Furthermore, glycaemia and blood pressure were measured at the time of hospital admission at 6 hrs and at 24 hrs; plasma creatinine was calculated at 6 hrs after admission, and urine specific gravity and ions (urine collection with a bag for incontinent patients and urine jet for the other patients) at 6 hrs after admission. Urine osmolarity was extrapolated from urine specific gravity (16).

Both blood ions and glycaemia were determined with the cooximeter ABL 700 Series by Radiometer Copenhagen, blood pressure was measured with an electronic sphingomanometer Pulsemate BX 5 by Colins Electronics, and urine biochemistry and specific gravity were calculated with Cobas 6000 by Roche.

Hyponatremia was defined as a plasma sodium concentration <135 mEq/L, moderate hyponatremia as a concentration <130 mEq/L, severe hyponatremia as a concentration <125 mEq/L, and hypernatremia as a concentration >145 mEq/L (15). Hypertension was defined as average systolic blood pressure or diastolic blood pressure higher than (or equal to) 95th percentile for gender, age, and height on three measurements in each control (17).

Sample Size Calculation. Sample size calculation was based on the primary dependent end point of the study. The estimated incidence (7) of iatrogenic hyponatremia in the control group was 10%, and a relative difference of 25% in the incidence of hyponatremias between both groups was considered clinically relevant. Taking into account an alpha error of 0.05 and a power of 80% to detect this difference and by using the arc sine approximation, the sample size required was calculated to be 102 patients plus patient losses. On the basis of the average duration of hospitalization at our unit and the mean duration of fluid therapy, we estimated a loss rate of 20%; thus, the required sample was established at 122 patients.

Randomization. By using the "Randomization" function of the MS-Excel XP program of Windows, a binary series with randomized numbers were generated following the procedure described by Friedman et al. (18). To achieve a similar number of patients in both groups, this procedure creates the sequence by using balanced block sampling. To ensure concealment, two block sizes are used: one of four elements and one of six elements.

Statistical Analysis. Statistical analysis was based on the intention to treat. For the calculations we used the program SPSS 12 for Windows XP. Categorical end points are described with the numerical count (percentage) of each category and are then compared with the chi-square test (if all application criteria are met) or with Fisher's exact test (if the criteria are not met). Continuous end points are represented by Tukey's box-plot graphs. If the continuous end points are normal ($p > 0.05$ in Shapiro-Wilk's test), they are described as the mean value ± SD, and are compared using the Student's t test after verifying the assumption of equality of variances using Levene's test. If the continuous end points are not normal, they are described as the median (P25, P75) and are compared using the nonparametric Mann-Whitney U test. During the whole study a statistical significant limit of $p \leq 0.05$ is accepted.

A Bayesian analysis has also been conducted to calculate the risk of hyponatremia and hypernatremia in each group and at each time of ion determination. In the analysis, sample data have been entered using a binomial distribution for percentages and a normal distribution for continuous variables. The *a priori* noninformative reference distribution was the Beta (1/2,1/2) distribution for percentages and the uniform distribution for continuous variables. The results are shown using

the *a posteriori* distribution obtained by applying the Bayes' theorem. The measurement of probabilities has been done integrating the *a posteriori* distribution.

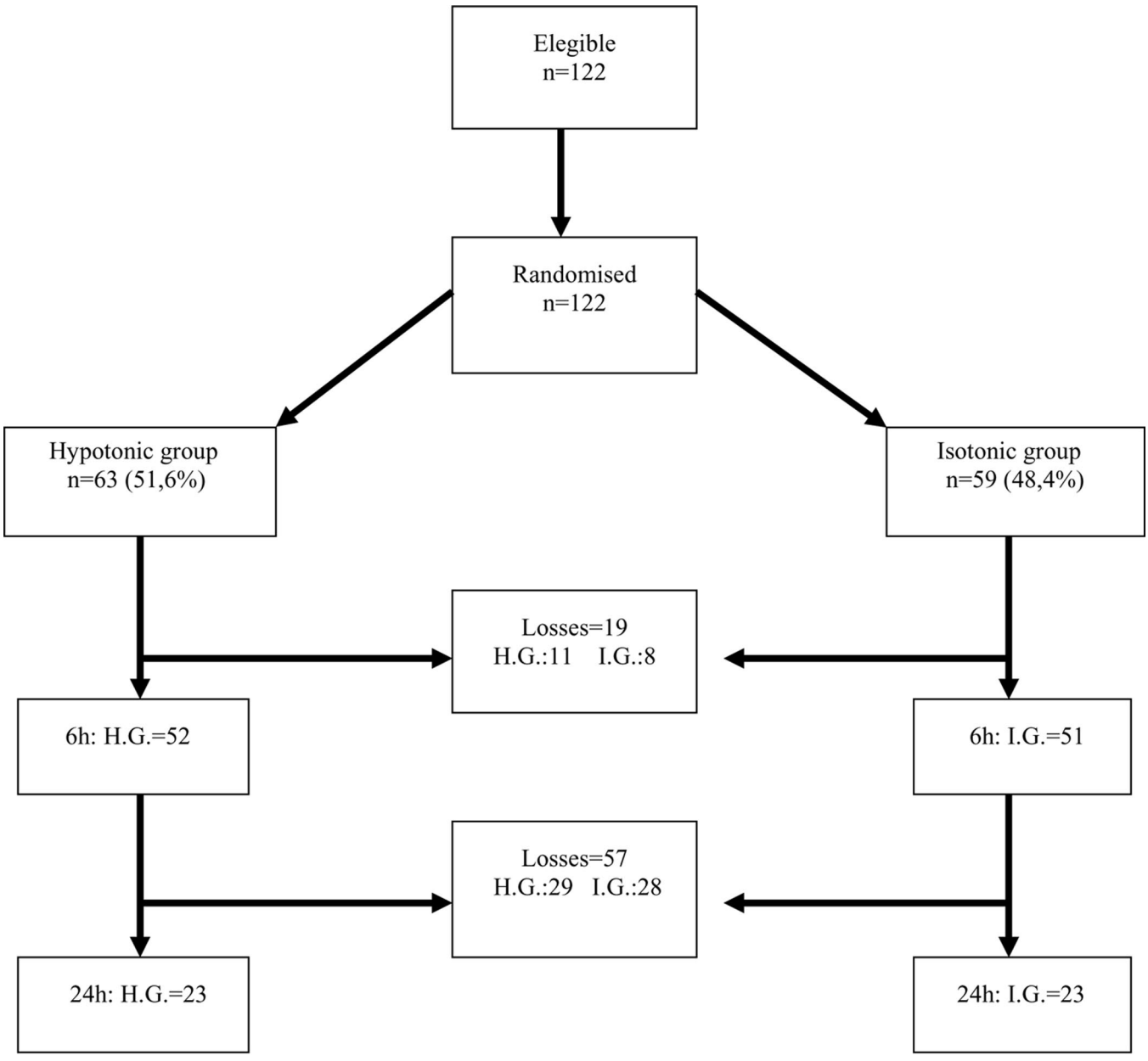
RESULTS

Figure 1 represents the flow chart of the patients included in the study. A total of 122 patients were included. No one refused to enter into the study. The randomization process finally allocated 63 patients to the hypotonic group and 59 patients to the isotonic group. Table 1 shows that the randomization generated two cohorts that were completely comparable and interchangeable as regards their baseline characteristics before study group allocation.

In the first control (at 6 hrs), a total of 19 subject discontinuations were reported: 18 because physicians considered that maintenance intravenous fluids could be interrupted before 6 hrs, and one because of requiring emergency surgery after randomization. Table 2 analyzes the loss of patients in both cohorts in this control. There was no significant difference in the number of patients discontinued or in the baseline characteristics of the population in each group.

In the control at 24 hrs 57 losses were reported: 48 because maintenance fluids could be interrupted earlier, eight because natremia levels were <130 mEq/L, and one because of emergency surgery following randomization. Table 3 analyses the loss of patients in both cohorts in this second control: again, it may be assumed that the loss of patients occurred randomly in both groups.

Tables 4 and 5 summarize the results obtained in the first and the second con-



H.G.: Hypotonic group; I.G.: Isotonic group.

Figure 1. Flow chart of the subjects participating in the study and follow up.

Table 1. Patients' characteristics at baseline

	Total	Hypotonic Group	Isotonic Group	*p*
No. patients randomized	122	63	59	
Male (%)	63 (51.6%)	28 (44.4%)	35 (59.3%)	0.11[a]
Age (yrs)	3.0 (1.0; 9.0)	3.0 (0.9; 7.0)	3.2 (1.3; 10.0)	0.32[b]
Weight (kg)	15.0 (8.0; 27.0)	14 (7.5; 25.0)	15 (10.0; 28.5)	0.26[b]
Patients with hypertension (%)	41 (33.6%)	20 (37.7%)	21 (42.0%)	0.66[c]
Serum sodium (mEq/L)	137.0 (134.0; 139.0)	137.0 (134.0; 139.3)	137.0 (134.0; 139.0)	0.75[b]
Patients with initial hyponatremia (%)	28 (23.0%)	15 (23.8%)	13 (22.0%)	1.00[a]
Serum potassium (mEq/L)	4.2 (3.5; 4.9)	4.3 (3.6; 4.8)	4.2 (3.4; 4.9)	0.90[b]
Serum glucose (mg/dL)/(mmol/L)	145.5 (110.5; 188.7)/8.07 (6.13;10.47)	141.0 (103.0; 196.5)/7.83 (5.72;10.91)	149.5 (112.0; 187.3)/8.30 (6.22;10.40)	0.73[b]
Time in intensive care unit (hrs)	23.5 (19.0; 24.0)	24 (19.5; 24.0)	22.5 (18.8; 24.0)	0.26[b]
Type of diagnosis				
Brain pathology and surgery	23 (18.8%)	13 (20.6%)	10 (16.9%)	0.70[c]
Thoracic pathology and surgery	22 (18.0%)	10 (15.9%)	12 (20.3%)	
Cardiac surgery	17 (13.9%)	11 (17.5%)	6 (10.2%)	
Abdominal surgery	41 (33.6%)	19 (30.1%)	22 (37.3%)	
Others	19 (15.6%)	10 (15.9%)	9 (15.2%)	
Total volume of infused fluids per weight (mL/kg/day)	61.7 (34.1; 85.1)	53.9 (30.0; 87.9)	64.9 (36.7; 84.5)	0.59[b]
Patients with hypernatremia	3 (2.5%)	3 (4.8%)	0 (0.0%)	0.24[a]

Categorical variables are described with a percentage (%) and continuous variables are described with a median (p25, p75).
[a]Fisher's exact test; [b]Mann–Whitney U test; [c]Pearson's chi-squared test.

Table 2. Characteristics of patients lost at the first control (6 hrs)

	Total	Hypotonic Group	Isotonic Group	*p*
No. patients randomized	122	63	59	
Percentage of loss				
Total	19 (15.6%)	11 (17.5%)	8 (13.6%)	0.63[b]
Percentage of male patients	8 (42.1%)	5 (45.5%)	3 (37.5%)	1.00[b]
Age (yrs)	2.0 (1.0; 6.0)	2.0 (0.7; 7.5)	2.0 (1.3; 3.0)	0.96[c]
Weight[a] (kg)	15.6 ± 9.2	15.9 ± 11.5	15.3 ± 4.3	0.92[d]
Type of diagnosis				
Brain pathology and surgery	1 (5.3%)	1 (9.1%)	0 (0.0%)	0.55[e]
Thoracic pathology and surgery	10 (52.6%)	6 (54.5%)	4 (50%)	
Cardiac surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Abdominal surgery	2 (10.5%)	2 (18.2%)	0 (0.0%)	
Others	6 (31.6%)	2 (18.2%)	4 (50%)	

Categorical variables are described with a percentage (%) and continuous variables are described with a median (p25, p75), except for [a]which is described with a mean ± SD.
[b]Fisher's exact test; [c]Mann–Whitney's U test; [d]Student's *t*-test; [e]Pearson's chi-squared test.

Table 3. Characteristics of patients lost at the second control (24 hrs)

	Total	Hypotonic Group	Isotonic Group	*p*
No. patients randomized	122	63	59	
Percentage of loss				
Total	57 (46.7%)	29 (49.1%)	28 (47.5%)	0.72[a]
Percentage of male patients	29 (50.8%)	13 (44.8%)	16 (57.1%)	0.57[a]
Age (yrs)	3.0 (1.0; 9.8)	3.0 (1.0; 6.0)	3.0 (1.7; 10.0)	0.97[b]
Weight (kg)	15.0 (10.0; 24.0)	15.0 (9.0; 21.0)	15.0 (11.3; 29.3)	0.67[b]
Type of diagnosis				
Brain pathology and surgery	7 (12.3%)	5 (17.2%)	2 (7.1%)	0.68[c]
Thoracic pathology and surgery	15 (26.3%)	8 (27.6%)	7 (25%)	
Cardiac surgery	1 (1.8%)	0 (0.0%)	1 (3.6%)	
Abdominal surgery	21 (36.8%)	10 (34.5%)	11 (39.3%)	
Others	13 (22.8%)	6 (20.7%)	7 (25%)	

Categorical variables are described with a percentage (%) and continuous variables are described with a median (p25, p75).
[a]Fisher's exact test; [b]Mann–Whitney's U test; [c]Pearson's chi-squared test.

Table 4. Results of the first control (6 hrs)

	Hypotonic Group	Isotonic Group	p
N	52	51	
Serum sodium (mEq/L)			
All[a]	136.4 ± 6.8	137.1 ± 3.7	0.52[d]
Brain pathology and surgery	136.0 (133.0; 139.0)	137.0 (132.8; 138.8)	0.88[e]
Thoracic pathology and surgery[a]	136 ± 6.9	136.9 ± 3.1	0.72[d]
Extracorporeal surgery[a]	141.7 ± 5.5	143.0 ± 2.0	0.63[d]
Abdominal surgery	134.0 (131.0; 136.5)	136.0 (133.0; 139.5)	0.03[e]
Patients with hyponatremia			
All	20/63 (31.7%)	15/59 (25.4%)	0.53[f]
Brain pathology and surgery	3/13 (23.1%)	2/10 (20%)	1.00[f]
Thoracic pathology and surgery	2/10 (20%)	2/12 (16.7%)	1.00[f]
Extracorporeal surgery	2/11 (18.2%)	0/6 (0%)	1.00[f]
Abdominal surgery	9/19 (47.4%)	9/22 (40.9%)	0.75[f]
Patients with moderate hyponatremia	4/63 (6.3%)	0/59 (0%)	0.12[f]
Patients with severe hyponatremia	4/63 (6.3%)	0/59 (0%)	0.12[f]
Serum potassium (mEq/L)	4.6 (3.7; 5.0)	4.2 (3.7; 5.0)	0.79[e]
Serum glucose (mg/dL)/(mmol/L)	129.0 (114.5; 190.1)/7.16 (6.35;10.55)	132.5 (116.0; 164.3)/7.35 (6.44;9.12)	0.96[e]
Creatinine (mg/dL)/(μmol/L)	0.3 (0.2; 0.5)/0.024 (0.018;0.040)	0.4 (0.3; 0.5)/0.032 (0.024;0.040)	0.27[e]
Urine sodium (mEq/L)	75.7 (38.5; 150.3)	127.5 (70.8; 185.7)	0.04[e]
Urine potassium (mEq/L)	49.0 (25.2; 86.2)	53.5 (31.8; 83.0)	0.33[e]
Urine osmolarity[b] (mOsm/L)	500 (400; 1000)	800 (400; 1040)	0.02[d]
Urine tonicity[c] (mmol/L)	144.4 ± 80.9	186.8 ± 86.8	0.03[d]
Percentage of side effects to IV fluids (other than electrolyte abnormalities)	0/63 (0%)	0/59 (0%)	
Patients with hypertension	15/63 (23.8%)	14/59 (23.7%)	0.72[g]
Patients with hypernatremia	4/63 (6.3%)	2/59 (3.3%)	0.68[f]
Serum sodium in patients with hypernatremia[a] (mEq/L)	148.3 ± 1.3	148.0 ± 2.8	0.88[d]

Categorical variables are described with a percentage (%) and continuous variables are described with a median (p25, p75), except for [a]which is described with a mean ± SD; [b]Estimated from urine specific gravity; [c]Sum of sodium and potassium in urine, in mEq/L; [d]Student's *t* test; [e]Mann–Whitney's U test; [f]Fisher's exact test; [g]Pearson's chi-squared test.

IV, intravenous; mg/dL, milligrams per deciliter; mEq/L, milliequivalents per liter; mOsm/L, milliosmols per liter; mmol/L, millimols per liter.

Table 5. Results at the second control (24 hrs)

	Hypotonic Group	Isotonic Group	p
N	23	23	
Serum sodium[a] (mEq/L)	136.2 ± 5.2	138.9 ± 3.6	0.02[b]
Patients with hyponatremia	13/63 (20.6%)	3/59 (5.1%)	0.02[c]
Patients with moderate hyponatremia	3/63 (4.8%)	0/59 (0%)	0.25[c]
Patients with severe hyponatremia	0/63	0/59	
Number of secondary effects to IV fluids (other than electrolyte abnormalities)			
Total	0/63 (0%)	2/59 (3.4%)	0.50[c]
Skin burns	0/63 (0%)	1/59 (1.7%)	
Hypoglycaemia (<60 mg/dL)	0/63 (0%)	1/59 (1.7%)	
Patients with hypertension	7/63 (11.1%)	7/59 (11.9%)	0.92[d]
Patients with hypernatremia	1/63 (1.6%)	1/59 (1.7%)	1.00[c]

Categorical variables are described with a percentage (%) and continuous variables are described with a median (p25, p75), except for [a]which is described with a mean ± SD.

[b]Student's *t* test; [c]Fisher's exact test; [d]Pearson's chi-squared test.

IV, intravenous.

trols of the study. In the first control, no statistically significant differences between groups were found in sodium values and percentages of hyponatremia. However, if we divide the patients by the type of diagnosis we observed that, in the subgroup undergoing abdominal surgery, natremia levels were lower in the group receiving hypotonic fluids (134 mEq/L compared to 136 mEq/L; $p = 0.03$). As to urine samples, sodium levels, osmolarity, and tonicity were higher in the isotonic group. No side effects directly related with intravenous fluid infusion were observed in any of the groups, other than electrolyte abnormalities. No differences in systolic and diastolic blood pressure values, or in the percentage of hypernatremia, were found between the two groups.

In the second control, patients included in the hypotonic group showed lower natremia values than those included in the isotonic group (136.2 ± 5.2 mEq/L compared with 138.9 ± 3.6 mEq/L; $p = 0.02$) and a higher percentage of hyponatremias (20.6% compared with 5.1%; $p = 0.02$) at 24 hrs. Figure 2 shows the box-plot graph comparing natremia values between the two groups. Regarding moderate hyponatremia, no patients in the isotonic group reported natremia values <130 mEq/L, as opposed to 4.8% of patients in the hypotonic group. This difference was not statistically significant ($p = 0.25$). In this control, no severe hyponatremias were observed in any of the two groups. In the isotonic group, one patient suffered a second-degree skin burn caused by an extravasation of the fluid infused and another one suffered an episode of hypoglycemia. No further side effects directly related with the infusion of intravenous fluids, other than electrolyte abnormalities, were reported. No statistically significant differences in the number of side effects were observed

between the two groups. No differences were observed in the number of hypernatremias or in blood pressure values between the two groups of the study.

Figures 3 and 4 show the Bayesian analysis performed to evaluate the probability of hyponatremia and hypernatremia in both groups. At 6 hrs following the initiation of intravenous fluid therapy, the probability of hyponatremia in the hypotonic group was 0.073, whereas in the isotonic group this probability was <0.001. The probability of hypernatremia at 6 hrs was <0.001 in both groups. At 24 hrs, the probability of hyponatremia in the hypotonic group increased to 0.089, whereas in the isotonic group this probability continued to be <0.001. In this control, the probability of hypernatremia in both groups was also <0.001.

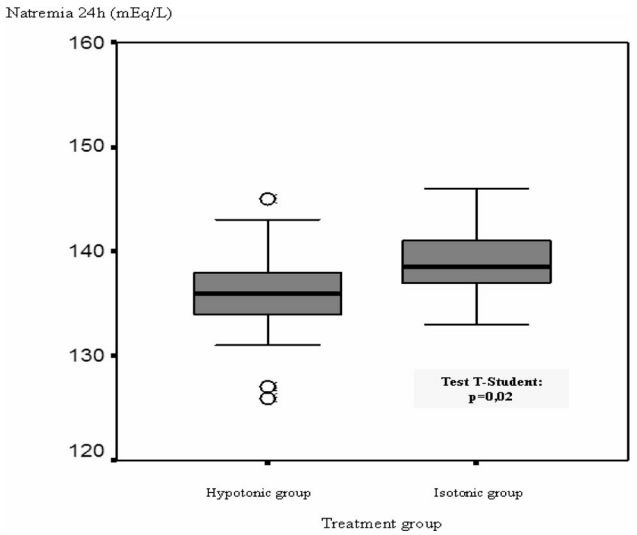
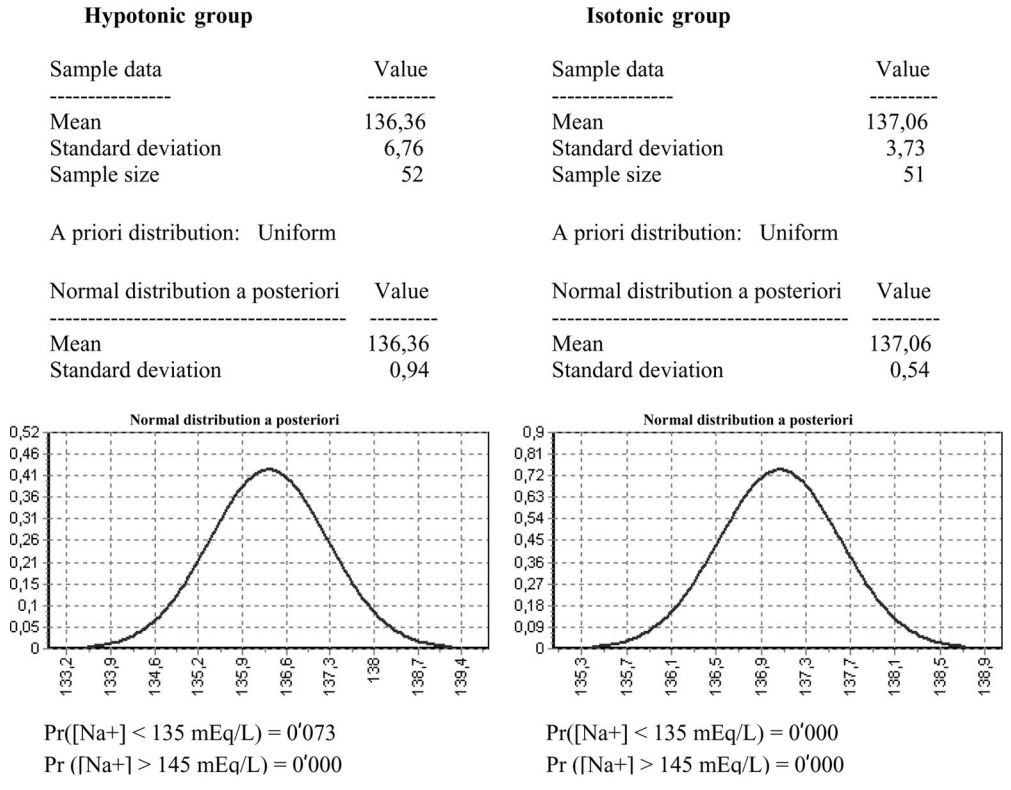


Figure 2. Box-plot graph comparing natremia values in both groups at 24 hours.

DISCUSSION

This study demonstrates that the use of isotonic solutions as maintenance fluid therapy prevents iatrogenic hyponatremia in patients hospitalized in pediatrics intensive care unit. We have observed that after 24 hrs of infusion, patients receiving hypotonic fluids had lower natremia levels and a higher incidence of hyponatremia (number need to harm [confidence interval (CI) 95%] = 7[4; 25]). This result confirms the hypothesis suggested by Hoorn et al. (6) and confirmed in a recent meta-analysis (19) indicating that the administration of hypotonic fluids was the most relevant risk factor for iatrogenic hyponatremia in pediatrics. Neville et al. (20) have also verified, in a randomized trial, that the use of isotonic fluids for rehydration prevents iatrogenic hyponatremia in pediatric patients with acute gastroenteritis. Other two clinical studies on postsurgical pediatric patients, one randomized (21) and another one nonrandomized (11), have also been published. In these studies, a significant reduction of natremia in children receiving hypotonic fluids was also reported.

No significant difference was found in natremia or the percentage of hypo-



Pr([Na+]<135 mEq/L): hyponatremia probability; Pr([Na+]>145 mEq/L): hypernatremia probability.

Figure 3. Study using Bayesian statistics to assess the risk of hyponatremia and hypernatremia at first control (6 hours).

Hypotonic group

Sample data	Value
Mean	136,16
Standard deviation	5,16
Sample size	23

A priori distribution: Uniform

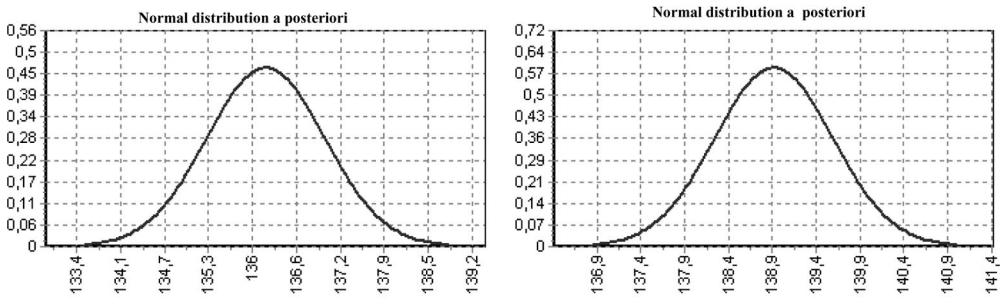
Normal distribution a posteriori	Value
Mean	136,36
Standard deviation	0,86

Isotonic group

Sample data	Value
Mean	138,93
Standard deviation	3,61
Sample size	23

A priori distribution: Uniform

Normal distribution a posteriori	Value
Mean	138,93
Standard deviation	0,67



Pr([Na+] < 135 mEq/L) = 0′089
Pr ([Na+] > 145 mEq/L) = 0′000

Pr([Na+] < 135 mEq/L) = 0′000
Pr ([Na+] > 145 mEq/L) = 0′000

Pr([Na+]<135 mEq/L): hyponatremia probability; Pr([Na+]>145 mEq/L): hypernatremia probability.

Figure 4. Study using Bayesian statistics to access the risk of hyponatremia and hypernatremia at second control (24 hours).

natremia between both groups at 6 hrs following the initiation of the infusion. Nevertheless, the Bayesian analysis indicated that the risk of hyponatremia in patients receiving hypotonic fluids was 0.073 at 6 hrs and 0.089 at 24 hrs. In patients receiving isotonic fluids, this risk remained below 0.001 in both controls, thus suggesting that the hyponatremic effect of hypotonic fluids accumulates depending on the duration of the infusion.

When studying the subgroups per diagnosis, we observed that natremia levels at 6 hrs were already lower in patients undergoing abdominal surgery and receiving hypotonic fluids. This finding may be biased by the formulation of the fluids infused during surgery, but such information was not collected in our study. The randomized design of our study tried to avoid this confusion and, therefore, abdominal surgery may act as an accelerating factor of the hyponatremic effect of hypotonic fluids, a hypothesis that should be confirmed in future studies.

Iatrogenic hyponatremia increased morbidity and mortality of hospitalized patients (7–10). Twenty percent (CI 95% = 10%–30%) of patients treated with hypotonic fluids at the time of hospital admission suffered from some degree of intravenous fluid-induced hyponatremia, an incidence that was similar to that reported in observational studies (6, 7). Our clinical trial demonstrates that this risk may be prevented with the use of isotonic solutions in pediatric patients requiring maintenance fluid therapy. Hoorn et al. (6) recommend the use of isotonic fluids exclusively in patients with sodium levels below 138 mEq/L or undergoing surgery. Our data show that this recommendation may also be applied to all patients with the same characteristics than the population included in this study, because natremia values at the beginning of the study were between 130 and 150 mEq/L and patients had different medical and surgical pathologies.

In a retrospective review of 24,412 patients, Arieff et al. (7) calculated that the incidence of deaths among patients with iatrogenic hyponatremia was 8.4% (CI 95% = 1.85%–15.01%), and 1 of 12–54 patients with hospital-acquired hyponatremia would die, thus showing the clinical relevance of hypotonic fluid-induced disturbances.

Traditional guidelines and recommendations published 50 yrs ago (1) and later confirmed (14) are based on the oral administration received by lactating children and their urine sodium concentrations. This does not take into account the capacity of the digestive tract to act as a functional barrier and to actively take from its lumen the received elements depending on the body's requirements (22). When we administer fluids intravenously, i.e., nonphysiologically, all the infused elements directly pass to the intravascular space where a delicate tonicity balance determines the intravascular and extravascular spaces. To not disturb this balance, we should think that the amount of sodium administered per kilogram weight is not as relevant as the concentration per liter of volume infused, and that this should be the physiologic concentration of sodium in the extracellular space.

It has been suggested that the use of isotonic fluids could theoretically entail risks (23). The percentage of hypernatremia was not different between both groups either at 6 hrs or at 24 hrs. The Bayesian analysis of the two cohorts indicate that the probability of hypernatremia with any of the fluids assessed was

<0.001 during the study. The percentage of phlebitis and hypertension was not different between the two groups in any study control. Therefore, the supposed risks of isotonic solutions do not seem real in practice and should not affect the decision of using them.

Our recommendation is to use isotonic fluids as maintenance liquids from the beginning of fluid therapy in all patients who do not have important free water loss through the urine (diabetes insipidus) or previous plasma sodium abnormalities. It is also important to stress that no side effects because of the infusion of these fluids have been reported, either in pediatric or in adult patients. Our results support the recommendation by Holliday et al. (23) suggesting that isotonic fluids should be used for 6–12 hours in patients undergoing surgery to restore volemia and reduce the amount of antidiuretic hormone. However, they do not support the recommendation of changing isotonic fluids for hypotonic fluids after 12 hrs to avoid hypernatremia. The probability of inducing hypernatremia with the isotonic drip is very low (and the same as with the hypotonic drip), and replacing it with the hypotonic drip would increase the risk of hyponatremia. The main factor of iatrogenic hyponatremia is the maintenance of hypotonic fluids for >6 hrs of fluid therapy and, thus the protective effect of isotonic liquids is only found in long-term treatments. In addition, this type of fluids should be administered from the beginning in patients undergoing abdominal surgery, taking into account their higher tendency toward decreasing natremia.

The literature based on Stewart's acid–base approach predicts that the use of fluids with the same concentration of chloride and sodium ions induces metabolic acidosis (24). Two clinical trials (25, 26) have demonstrated that this prediction comes true in humans. In our study, we have not been able to assess the effects of the recommended regime of fluid therapy on pH, because the protocol did not include the routine measurement of blood pH. Although our results support the use of isonatremic maintenance fluids, it still has to be determined whether it would be more advisable to use fluids with more sodium than chloride (26).

The main limitation of this study is the relevant number of patients who withdrew from the study. This may be justified by the high number of patients not requiring fluid therapy for more than a few hours at our unit. Ethical reasons did not allow us to extend the hours of intravenous infusion, so we studied the losses to ensure that they had been distributed homogeneously between the two groups. No significant differences were found in any of the two controls. The intention-to-treat analysis and the homogenicity of the patients who withdrew from the study do not compromise the veracity of the results. Another source of bias is the fact that the study was not blinded, but blinding it would have increased too much the complexity of our study. Also, heterogeneity regarding the control therapy represents a study limitation, but we wanted to compare isotonic fluids with the standard practice used in our institution (2–4 mmol/kg/day, following Holliday's recommendations [1]).

In conclusion, this study demonstrates that isotonic fluids prevent iatrogenic hyponatremia without inducing a higher incidence of side effects. Therefore, these would be the maintenance fluids that should be selected for patients with no excessive and continuous loss of free water or previous plasma sodium abnormalities. The traditional recommendation by Holliday and Segar (1) should be reconsidered, and the amount of sodium administered with regards to the volume of the infusion and not per kilogram of weight of the children should be assessed. Furthermore, the higher risk of hyponatremia in patients undergoing abdominal surgery and receiving hypotonic solutions should be confirmed, and the isonatremic dilution to be used to minimize the risk of hyperchloremic acidosis should be determined.

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