

Effect of isotonic versus hypotonic maintenance fluid therapy on urine output, fluid balance, and electrolyte homeostasis: a crossover study in fasting adult volunteers

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Abstract

Background. Daily and globally, millions of adult hospitalized patients are exposed to maintenance i.v. fluid solutions supported by limited scientific evidence. In particular, it remains unclear whether fluid tonicity contributes to the recently established detrimental effects of fluid, sodium, and chloride overload.

Methods. This crossover study consisted of two 48 h study periods, during which 12 fasting healthy adults were treated with a frequently prescribed solution (NaCl 0.9% in glucose 5% supplemented by 40 mmol litre⁻¹ of potassium chloride) and a pre-mixed hypotonic fluid (NaCl 0.32% in glucose 5% containing 26 mmol litre⁻¹ of potassium) at a daily rate of 25 ml kg⁻¹ of body weight. The primary end point was cumulative urine volume; fluid balance was thus calculated. We also explored the physiological mechanisms behind our findings and assessed electrolyte concentrations.

Results. After 48 h, 595 ml (95% CI: 454–735) less urine was voided with isotonic fluids than hypotonic fluids ($P < 0.001$), or 803 ml (95% CI: 692–915) after excluding an outlier with 'exaggerated natriuresis of hypertension'. The isotonic treatment was characterized by a significant decrease in aldosterone ($P < 0.001$). Sodium concentrations were higher in the isotonic arm ($P < 0.001$), but all measurements remained within the normal range. Potassium concentrations did not differ between the two solutions ($P = 0.45$). Chloride concentrations were higher with the isotonic treatment ($P < 0.001$), even causing hyperchloraemia.

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Conclusions. Even at maintenance rate, isotonic solutions caused lower urine output, characterized by decreased aldosterone concentrations indicating (unintentional) volume expansion, than hypotonic solutions and were associated with hyperchloraemia. Despite their lower sodium and potassium content, hypotonic fluids were not associated with hyponatraemia or hypokalaemia.

Clinical trial registration. ClinicalTrials.gov (NCT02822898) and EudraCT (2016-001846-24).

Key words: electrolytes; fluid therapy; water-electrolyte balance

Editor's key points

- The physiological response to i.v. fluid therapy composition (tonicity, electrolytes, osmoles) and volume will determine risk of fluid overload.
- Daily administration of several litres of commonly used i.v. crystalloid fluids will lead to electrolyte–salt overload in surgical patients.
- This study found that an isotonic crystalloid fluid was associated with less urine output when compared with a hypotonic fluid.
- More care should be used when prescribing perioperative fluid therapy; this is crucially important when larger volumes are administered over more than 24 h.

Maintenance i.v. fluid solutions are prescribed to cover the daily need for water and electrolytes in patients who are unable to ingest food or fluids. Ideally, they also contain dextrose or glucose to prevent starvation ketosis while awaiting full (par)enteral nutrition. Although maintenance fluids are used daily in hospitals worldwide, the scientific evidence guiding clinical practice is strikingly limited. Current guidelines are based on older dietary reference values, which by their very nature concern only oral intake.^{1–3} Our understanding of the human organism's response to the tonicity of correctly dosed i.v. maintenance fluids remains an educated guess based on older physiological experiments.⁴ Previous studies showed that a large volume of isotonic fluid administered rapidly is excreted more slowly than an equal amount of a hypotonic solution.^{5–7} However, it remains unclear whether the tonicity of maintenance fluids could be a separate contributor to fluid overload and altered electrolyte concentrations. The scarce data on prescription practices demonstrate the frequent use of isotonic solutions, ignoring available guidelines.⁸

Important paediatric research emphasized the protective effect of isotonic maintenance solutions against hyponatraemia-induced morbidity compared with hypotonic solutions prescribed using the classical Holliday and Segar formula.^{9–12} Yet this use of isotonic fluids remains contested, even among paediatricians, some of whom have called for improved awareness of inappropriate (and appropriate, i.e. hypovolaemia-induced) secretion of anti-diuretic hormone (ADH) instead of redundantly salt loading a large number of children.^{13–14} Furthermore, the design of the abovementioned trials, all of which focused on the occurrence of hyponatraemia, provided no insights into the deleterious potential of salt-rich solutions. Even more controversially, some authors recently suggested extrapolating the routine use of isotonic maintenance fluids to the adult setting.¹⁵ Not only are the symptoms of potential hyponatraemia less dramatic in this population but also the detrimental effects of fluid and salt overload are well known in the care of surgical and critically ill adult patients.^{16–19}

We designed this study to test the hypothesis that isotonic fluids, even at maintenance rate, lead to lower urine output than their hypotonic counterparts. As a secondary end point, we explored possible physiological explanations by studying key players in volume regulation and osmoregulation. Furthermore, we aimed to investigate the impact of maintenance fluids on the serum concentration of various electrolytes, sodium, potassium, chloride, calcium, and phosphate. In many hospitals, it is routine practice to add hypertonic potassium chloride to maintenance fluids manually, although this is regarded as a high-risk medication.²⁰ Premixed solutions have a better safety profile, but most commercially available solutions contain potassium in lower-than-recommended doses. Strong ion difference, a marker of fluid-induced metabolic acidosis, was also assessed.

Methods

We conducted a single-blind crossover study in 12 healthy volunteers at the Antwerp University Hospital, Belgium. In order to be eligible for the study, participants had to be between 18 and 70 yr of age, with a BMI of between 17 and 45 kg m⁻² and an estimated glomerular filtration rate of >60 (ml⁻¹ min⁻¹ (1.73 m)⁻²).²¹ Exclusion criteria were acute medical illness in the 3 weeks before any of the study periods, the use of medication interfering with urine output, pregnancy, medical history of cardiac failure, malnourishment, diabetes mellitus, urological disease preventing complete emptying of the bladder, or any medical or non-medical issue preventing complaint-free fasting for 48 h. The study was approved by the hospital's Institutional Review Board (reference number 16/15/175) and the relevant national authority, the Federal Agency for Medicines and Health Products, Belgium (EudraCT 2016-001846-24). Participants were recruited through advertising in the investigators' institution. After selection, they received an information brochure and signed an informed consent form. The trial was registered at ClinicalTrials.gov (NCT02822898).

The study consisted of two study periods of 48 h, one for each maintenance solution. In order to ensure a balance in treatment sequence, subjects were matched by sex and BMI, after which each matched pair was allocated to the two treatment sequences as a block. To avoid any carryover effects, the two periods were separated by a 2 week washout period. The study was conducted in July and August 2016 in an air-conditioned facility to ensure a stable room temperature (~20 °C). Subjects were admitted at 08.00 h after a normal night's rest, having refrained from caffeinated drinks for at least 16 h and from any oral intake for at least 8 h before admission. Having asked the subjects to empty their bladders, we began infusion of the study fluid using an electronic infusion pump with an auditory alarm to detect obstruction. We blinded subjects to the treatment by concealing the fluids with opaque

covers. To correct for insensible losses during the night, subjects were given identical breakfasts shortly after admission, during which they drank a fluid volume five times their infusion rate (see below). From then on, they refrained from any oral intake for the rest of the study period. The infusion ran until the first urination after 48 h of fluid administration. Each study period was permanently medically supervised by a trained intensivist.

The study fluids were administered at 25 ml kg⁻¹ of body weight per day. When a subject's BMI was between 25 and 30 kg m⁻², we used the ideal body weight calculated using the formula of Devine.²² If the BMI was >30 kg m⁻², the adjusted body weight was calculated by increasing the ideal body weight by 25% of the difference between the actual and ideal body weights. The isotonic solution was NaCl 0.9% in glucose 5% with an added 40 mmol of potassium chloride 7.45% (osmolality 614 mOsm litre⁻¹; tonicity 373 mOsm litre⁻¹), so that a fluid volume of 25 ml kg⁻¹ per day would represent a daily potassium dose of 1 mmol kg⁻¹ of body weight. Notably, the addition of potassium chloride essentially renders this solution hypertonic, although potassium has a negligible effect on tonicity after administration. As for the hypotonic solution, we used a commercially available premixed solution (Glucion 5%®; Baxter Healthcare, Deerfield, IL, USA) containing sodium (54 mmol litre⁻¹), potassium (26 mmol litre⁻¹), chloride (55 mmol litre⁻¹), phosphate (6.2 mmol litre⁻¹), magnesium (2.6 mmol litre⁻¹), and lactate (25 mmol litre⁻¹; osmolality 447 mOsm litre⁻¹; tonicity 169 mOsm litre⁻¹).

The primary end point was cumulative urine volume over the course of 48 h; fluid balance was thus calculated. Subjects

emptied their bladders as the need arose, day or night. The exact urinary volume was determined by dividing its weight by its point-of-care-assessed density. Secondary end points were markers of volume regulation (the mineralocorticoid hormone aldosterone, urinary sodium, and serum albumin concentration) and osmoregulation (serum and urine osmolality, serum ADH, and thirst), and the serum concentration of clinically important electrolytes: sodium, potassium (especially as the hypotonic fluid contained a lower-than-guideline-recommended dose), chloride, phosphate, and calcium. Strong ion difference was also assessed.²³ Clinical parameters were collected mainly for safety reasons and body weight as a back-up primary end point. In summary, the following variables were assessed. Each urine void was sampled for measurement of urinary osmolality, sodium, potassium, and chloride. At baseline (t₀) and every 12 h (t₁₂, t₂₄, t₃₆, and t₄₈), we assessed body weight, blood pressure, heart rate, and a thirst score on a scale from 0 to 5. At t₀, t₂₄, and t₄₈, blood was obtained for serum sodium, potassium, chloride, osmolality, magnesium, calcium, phosphate, albumin, ADH, and aldosterone, with additional assessments of sodium, chloride, and potassium at t₁₂ and t₃₆. Strong ion difference was calculated as: Strong ion difference = [Na⁺]+[K⁺]+[Ca²⁺]+[Mg²⁺]-[Cl⁻].²³ The technicalities and normal ranges of the laboratory analyses are reported in the Supplementary material (Table S1). The subjects' usual dietary salt intake was approximated by assessing urinary sodium output by means of a 24 h urine collection 3–4 weeks after completion of the study.

Statistical analyses were performed using Stata 14 (StataCorp LP, College Station, TX, USA). Based on the literature, we assumed mean urinary outputs of 1250 ml for hypotonic solutions and 1050 ml for isotonic solutions during the trial period, both with an SD of 200 ml and an inpatient correlation of 0.5.⁶ Using simulation (10 000 trials), we estimated that a sample size of 10 would give the study a power of 80% to detect a 200 ml difference in urine output between infusions with a two-sided α set at 5%. We included two extra subjects to compensate for unexpected dropouts. An ANOVA of the area under the urinary output curve showed no sequence or period effects, so these were excluded from any further analysis. Absence of a carryover effect was assumed. Next, a random effects model was fitted for the primary end point, cumulative urine volume over the course of 48 h, with treatment, time, and their interaction as fixed effects and time as a random slope for each subject. Adjustment for body weight type (actual, ideal, adjusted) was evaluated using likelihood ratio tests and omitted in the absence of model improvement. The same procedure was followed for fluid balance and the more generalizable fluid balance per kilogram of actual body weight. Effect size was evaluated at t₄₈. The difference in laboratory and clinical values (e.g. thirst score) between the two solutions was assessed with a random intercept model using treatment as fixed effect, the baseline value as a covariate, and all subsequent values as outcome. We fitted per-treatment mixed models using time (categorical) as a fixed effect and subject as a random effect to assess the difference in serum values since t₀ within each treatment arm. Dunnett-adjusted P-values were used to correct for multiple testing. Statistical significance was set at a P-value of <0.05 (two-sided) for all tests. The results are reported with their 95% confidence intervals (CIs).

Results

The subjects' characteristics and details of their fluid therapy are presented in Table 1. The effect of treatment on cumulative

Table 1 Characteristics of the study population at the start of the first study period (n=12; 50% female) and the fluids administered during the two study periods

Subject characteristics	Mean (SD)	Range
	Age (yr)	35 (10)
Body weight (kg)	84 (31)	52–142
Height (cm)	173 (12)	154–191
BMI (kg m ⁻²)	27 (8)	19–45
Systolic blood pressure (mm Hg)	132 (17)	98–160
Estimated glomerular filtration rate ²¹ (ml min ⁻¹ (1.73 m ⁻²))	110 (13)	91–130
Dietary sodium intake (mmol day ⁻¹); 24 h urine collection	133 (61)	53–249
Oral fluid intake at start of study period (ml)	364 (85)	245–521
Infusion rate during first study period (ml h ⁻¹)	73 (17)	49–102
Fluid therapy characteristics per day	Isotonic period	Hypotonic period
	Mean (SD)	Mean (SD)
Administered volume (ml day ⁻¹)	1731 (410)	1732 (411)
Administered sodium (mmol day ⁻¹)	267 (63)	94 (22)
Administered chloride (mmol day ⁻¹)	323 (77)	95 (23)
Administered potassium (mmol day ⁻¹)	67 (16)	45 (11)

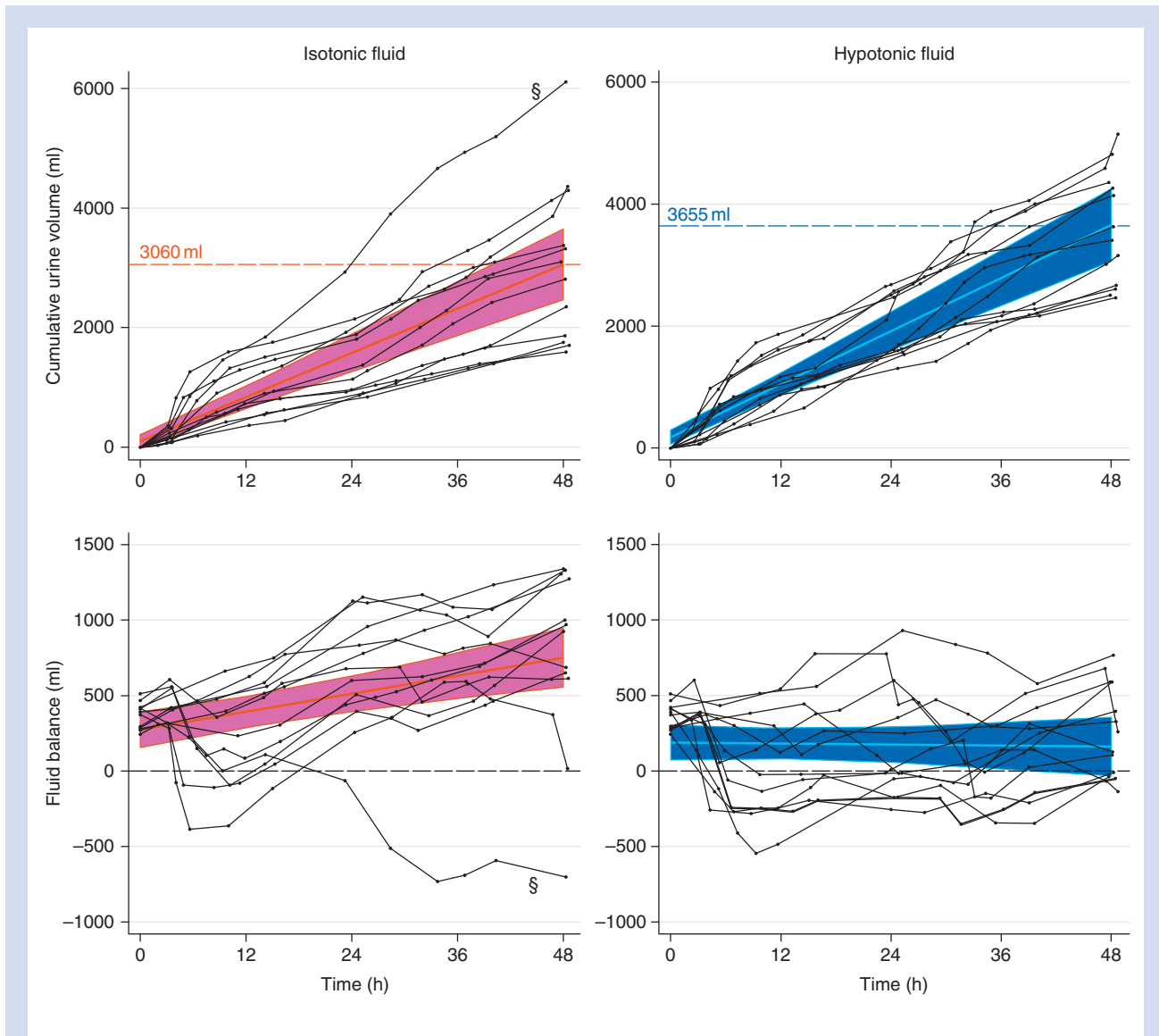


Fig 1 Cumulative urine volume (primary end point) and fluid balance over the course of each study period. Black lines are individual observations per subject. Coloured lines are the marginal means estimated using the mixed effects model; the shaded areas represent 95% confidence intervals. Dashed lines are predicted values at 48 h (t_{48}). §Outlier with exaggerated natriuresis; see text for details. The positive fluid balance at t_0 is attributable to oral fluid intake (see Table 1).

urine volume and fluid balance is shown in Fig. 1. In the isotonic treatment arm, the cumulative urine output at t_{48} (3060 ml; 95% CI: 2474–3647) was significantly lower than in the hypotonic treatment arm (3655 ml; 95% CI: 3069–4242; $P < 0.001$); we observed a mean difference of 595 ml (95% CI: 454–735). This finding was reflected in the fluid balance, which was estimated to be 590 ml (95% CI: 450–729) or 8.9 ml kg^{-1} of actual body weight (95% CI: 7.2–10.5) higher at t_{48} with isotonic treatment ($P < 0.001$). The raw data (black lines) revealed a clear outlier (§) characterized by an exceptionally large diuresis and a negative fluid balance in the isotonic arm. It is likely that this subject developed the exaggerated natriuresis sometimes seen in mild essential hypertension after the administration of saline.^{24–25} After omitting this subject from the subsequent sensitivity

analysis, the difference in predicted urine output between the two solutions increased to 803 ml (95% CI: 692–915) and the difference in fluid balance to 794 ml (95% CI: 681–906) or 10.8 ml kg^{-1} (95% CI: 9.3–12.4).

On a physiological level, we made separate assessments of the processes responsible for regulating effective circulating volume (Fig. 2) and osmolality (Fig. 3). Figure 2 clearly shows that aldosterone concentrations were significantly lower ($P < 0.001$) with isotonic treatment, as further illustrated by significantly higher concentrations of urine sodium ($P < 0.001$) and osmolality ($P = 0.01$). Serum albumin, which has been used as an experimental marker of plasma expansion, was lower with isotonic fluids ($P = 0.01$).²⁶ Serum osmolality ($P = 0.67$) and ADH ($P = 0.22$) did not differ significantly between and within solutions (Fig. 3). Thirst

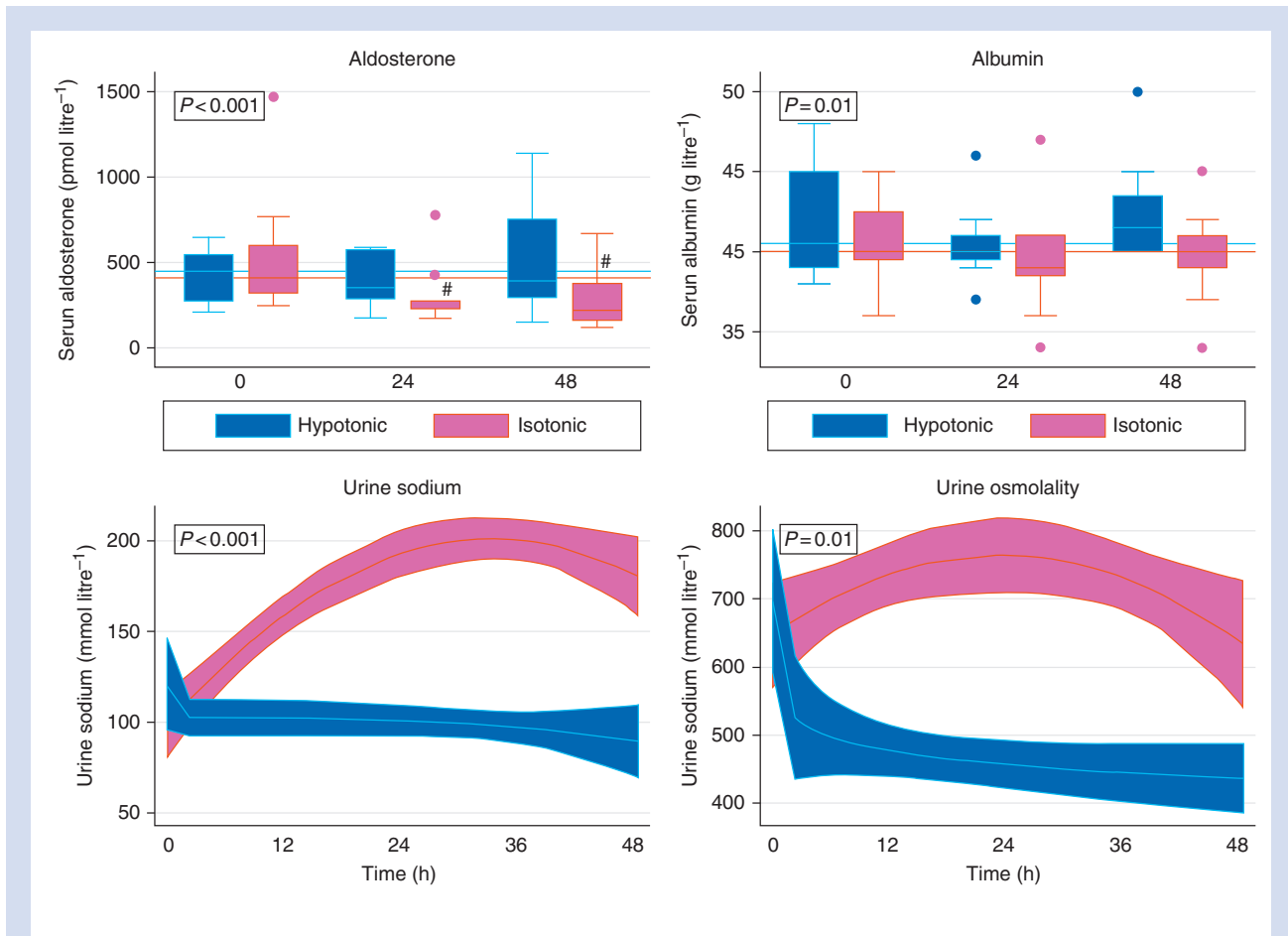


Fig 2 Physiological factors involved in the regulation of effective circulating volume. In-graph P-values are for the difference between the two fluids. #Significantly different from t_0 on a fluid-specific level ($P < 0.05$). Coloured lines indicate the median value at t_0 for each fluid. For representational purposes, urinary sodium and osmolality are the raw data shown as fractional polynomial prediction plots; shaded areas represent 95% confidence intervals.

score, although increasing with both treatments, was not different between the two solutions ($P = 0.69$).

The impact of each solution on the serum concentration of the various electrolytes is summarized in Fig. 4. No hyponatraemia or hypernatraemia (< 135 or > 145 mmol litre⁻¹) was observed during the study. Serum sodium concentrations were significantly higher with the isotonic treatment than the hypotonic treatment (1.2 mmol litre⁻¹; 95% CI: 0.7–1.7; $P < 0.001$), but no significant change from baseline values was observed with either solution. Serum potassium concentrations did not differ significantly between the two solutions ($P = 0.45$). One episode of hyperkalaemia (> 5 mmol litre⁻¹) was encountered with each of the treatments. Chloride concentrations were significantly higher with isotonic treatment than with hypotonic treatment (1.7 mmol litre⁻¹; 95% CI: 1.2–2.2; $P < 0.001$); the increase in the isotonic arm was significantly different from baseline at t_{12} , t_{24} , and t_{48} , where six of 48 assessments after t_0 (13%) exceeded the normal range. Strong ion differences were significantly lower with isotonic treatment (0.9 mEq litre⁻¹; 95% CI: 0.2–1.6; $P = 0.01$) and changed from baseline. For the hypotonic treatment, phosphate ($P < 0.001$) and calcium ($P = 0.01$) concentrations were significantly higher, although their serum concentrations largely remained within the normal range.

Discussion

Despite our growing awareness of the detrimental effects of perioperative volume, salt, and chloride overload, fluid research has focused almost exclusively on the resuscitation setting. Surprisingly, given their widespread use, this appears to be the first study to assess the effect of the tonicity of commonly prescribed maintenance solutions. This important characteristic of i.v. fluids is determined by the number of solutes to which cell membranes are impermeable. Despite contributing to the *in vitro* osmolality of a fluid, glucose crosses cell membranes rapidly after i.v. administration. As a result, only dissolved electrolytes contribute to the tonicity of a solution and exert an osmotic pressure gradient. Previous studies demonstrating the clinical impact of salt-poor perioperative maintenance therapy invariably involved the restriction of fluid volume, thereby precluding conclusions about the specific role of fluid tonicity.^{16 17} Although guidelines recommend a hypotonic maintenance strategy, the scarce observational data demonstrate that this advice is frequently ignored.⁸ We compared a premixed hypotonic fluid with a solution containing NaCl 0.9% in glucose 5% to which 40 mmol of potassium chloride was added manually to supply the subjects with the recommended amount potassium

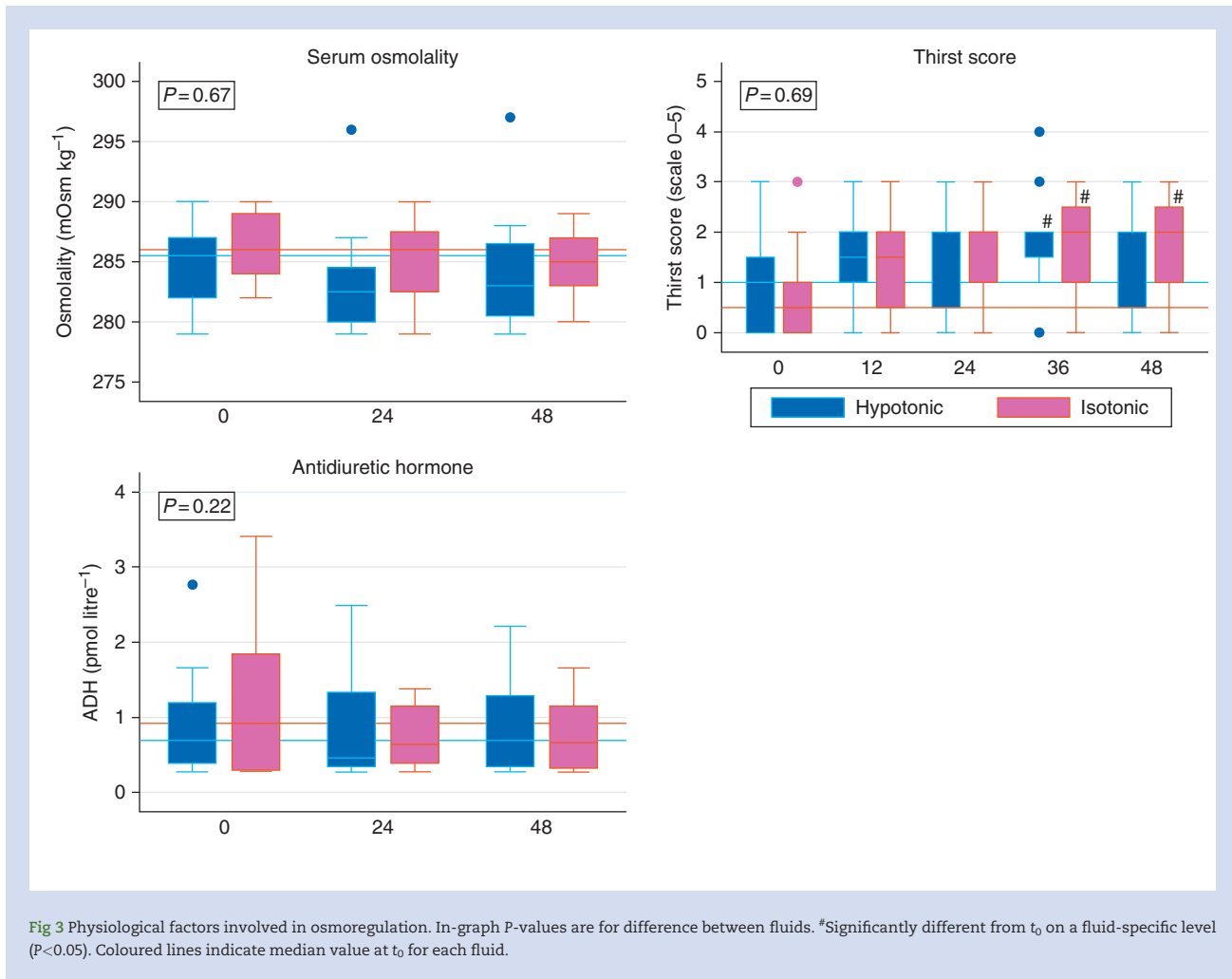


Fig 3 Physiological factors involved in osmoregulation. In-graph P-values are for difference between fluids. #Significantly different from t₀ on a fluid-specific level (P<0.05). Coloured lines indicate median value at t₀ for each fluid.

of 1 mmol kg⁻¹ of body weight per day.¹ Although conveniently termed isotonic, it should be acknowledged that this widespread practice essentially renders this solution hypertonic.

Our study not only showed that urine output was significantly lower after 2 days of isotonic vs hypotonic maintenance therapy, but also that the observed effect was remarkably substantial; isotonic retention exceeded 10 ml kg⁻¹ of body weight. Previous evidence of the morbidity associated with a weight gain of 3 kg during a typical perioperative period underscores the importance of this finding.¹⁶ The stable fluid balance we observed in the absence of increased aldosterone suggests that both the fluid volume and its sodium content are appropriate during hypotonic treatment. As we followed our subjects for only 2 days, however, it is unclear at what point a new steady state (characterized by renewed correspondence between intake and renal sodium excretion) would be reached. Based on previous dietary experiments, we can assume that fluid retention would persist for 3–5 days.⁴ Even then, the contracted fluid gain would be maintained until several days after the cessation of the increased sodium administration.⁴

We explored several markers of volume regulation and osmoregulation, the two main adaptive physiological mechanisms that are potentially responsible for the observed findings. Osmoregulation did not appear to play a major role because

serum osmolality, serum ADH, and thirst were not influenced by the type of the infusion fluid. On the contrary, the observed fluid retention with isotonic treatment could be explained by the reduction in aldosterone concentration, which acts as a marker of expanded effective circulating volume.⁴ This was further illustrated by the enhanced urinary sodium excretion and hinted at by the lower albumin concentrations in this treatment arm. We firmly believe that volume expansion is not the purpose of a routine maintenance prescription. Although it is usually the result of ADH secretion, the increase in urine osmolality can also be explained by isotonic plasma expansion without exceeding the osmoreceptor threshold. It is the consequence of compensatory water reabsorption at the level of the collecting tubule of the nephron after the reduced reabsorption of glomerular filtrate in the proximal tubule.²⁷ Likewise, decreased proximal tubular reabsorption is the most plausible explanation for the lower serum calcium concentrations during isotonic treatment.⁴

Despite the large difference in the sodium content of the two solutions, no abnormal sodium concentrations were encountered, and no significant variation from baseline value was observed. Of course, the incidence of inappropriate or appropriate ADH secretion is virtually non-existent in healthy subjects, and our finding does not contradict recent findings on paediatric maintenance

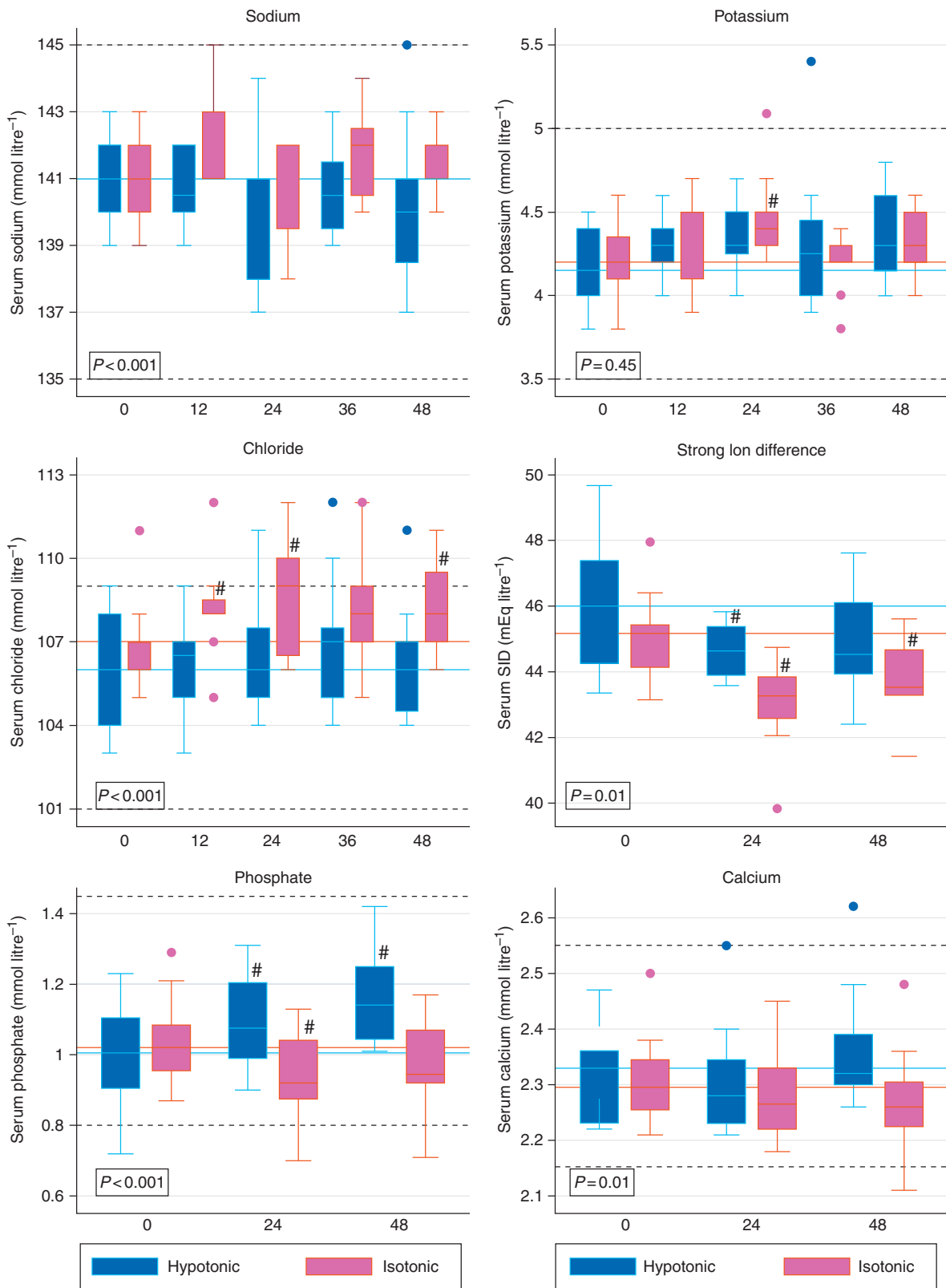


Fig 4 Serum concentration of various electrolytes and strong ion difference (SID) over the course of both study periods. In-graph P-values are for the difference between the two fluids. #Significantly different from t₀ on a fluid-specific level (P < 0.05). Black dashed lines represent the normal range of the electrolytes. Coloured lines indicate the median value at t₀ for each fluid.

prescription.^{9 10} However, as these studies considered the incidence of hyponatraemia in isolation, their conclusions might overlook the potentially important detrimental effects of salt-rich solutions. Our data indicate that these solutions could expose patients to unintended plasma expansion and fluid retention, even at maintenance rate; the consequences of this fact require further examination. Current guidelines recommend the administration of 1 mmol of potassium per kilogram of body weight, but the 26 mmol litre⁻¹ content in the hypotonic solution was sufficient to keep serum potassium concentrations unchanged from baseline and well within the normal range. The two episodes of hyperkalaemia recorded in a total of 120 measurements are likely to have been coincidental, especially as they were encountered in both treatment arms.

Chloride was the only electrolyte affected substantially by the isotonic solution, even frequently causing hyperchloraemia and a decreased strong ion difference, an established cause of metabolic acidosis.²⁸ It is common practice to add potassium manually in the form of concentrated potassium chloride to infusion fluids. In our study, this resulted in the administration of a remarkable 323 (77) mmol of chloride per day with the isotonic treatment [*vs* 95 (20) mmol using the hypotonic fluid]. The potential importance of these findings is illustrated by a recent study demonstrating the association between a chloride-rich fluid strategy and a higher incidence of acute kidney injury in critically ill patients.²⁹ Recently, a large chloride load was also shown to be associated with an unfavourable impact on various renal parameters in healthy volunteers.^{30 31} It is plausible that the ill-considered prescription of maintenance solutions is responsible for a substantial portion of iatrogenic chloride load, perhaps more so than resuscitation fluids, which are better researched but used for shorter periods.

Our study had certain limitations. First, to be able to measure the effect size as precisely as possible, we designed the study as a crossover experiment including only healthy volunteers rather than patients. Although we attempted to counteract this issue by selecting broad inclusion criteria, mimicking real life as closely as possible, the applicability of our findings to certain patients is unclear. In particular, the management of maintenance fluids in patients who are already fluid expanded or have renal failure requires exploration. The role of essential hypertension also remains unclear, as exaggerated natriuresis was clearly present in one of our subjects who had not previously been diagnosed with hypertension.²⁵ The extent and incidence of this phenomenon is unknown. Nonetheless, we believe our findings could easily be extrapolated to the majority of hospitalized patients in view of the 48 h fasting setting that resembles the clinical use of maintenance therapy. Finally, it is difficult to assess the definitive clinical impact of our findings, because the exact mechanisms behind the deleterious effect of fluid and salt overload require elucidation in many patient populations, including the critically ill. Only a set of well-designed clinical trials, performed in different subgroups, will be able to clarify this issue.

Conclusions

At the guideline-recommended dose, isotonic vs hypotonic maintenance solutions caused the retention of a potentially clinically relevant amount of fluid, characterized by decreased serum aldosterone concentrations that indicate volume expansion, which is not the intent of maintenance fluid therapy. In the absence of appropriate or inappropriate secretion of ADH, the hypotonic solution did not cause sodium abnormalities and,

despite its lower potassium content of 26 mmol litre⁻¹, serum potassium concentrations remained well within normal limits. The use of NaCl 0.9% supplemented by hypertonic potassium chloride caused a substantial chloride load and hyperchloraemia. In view of the widespread use of maintenance fluids, trials with carefully chosen end points are needed to address their safety in different clinical settings.

Authors' contributions

Study design: N.V.R., T.V.d.W., T.D.W., A.V.C., K.D., W.V., P.J., M.M.

Drafting the protocol: N.V.R., T.V.d.W., P.J.

Advice on the statistical analysis: E.R., T.V.d.W.

Advice on the physiological explanation behind the findings: T.D.W., A.V.C., W.V.

First draft of the manuscript: N.V.R.

Study coordinator and guarantor: N.V.R.

All authors have read and approved the final draft. All authors had full access to all of the data.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

N.V.R. has received speaker's fees from Baxter Belgium and resided in a medical advisory board organized by Baxter Healthcare, USA. M.M. reports speaker's fees from Maquet (Getinge Group) and is member of the medical advisory board. N.V.R. and M.M. are co-chairmen of the International Fluid Academy, a not-for-profit organization promoting education on fluid management and haemodynamic monitoring that received sponsoring from the industry. The other authors declare no conflicts of interest.

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