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Clinical Investigation

CLINICAL INVESTIGATION

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 premixed 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 antidiuretic 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