ORIGINAL

154 compared to 54 mmol per liter of sodium in intravenous maintenance fluid therapy for adult patients undergoing major thoracic surgery (TOPMAST): a single-center randomized controlled double-blind trial

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Abstract

Purpose: To determine the effects of the sodium content of maintenance fluid therapy on cumulative fluid balance and electrolyte disorders.

Methods: We performed a randomized controlled trial of adults undergoing major thoracic surgery, randomly assigned (1:1) to receive maintenance fluids containing 154 mmol/L (Na154) or 54 mmol/L (Na54) of sodium from the start of surgery until their discharge from the ICU, the occurrence of a serious adverse event or the third postoperative day at the latest. Investigators, caregivers and patients were blinded to the treatment. Primary outcome was cumulative fluid balance. Electrolyte disturbances were assessed as secondary endpoints, different adverse events and physiological markers as safety and exploratory endpoints.

Findings: We randomly assigned 70 patients; primary outcome data were available for 33 and 34 patients in the Na54 and Na154 treatment arms, respectively. Estimated cumulative fluid balance at 72 h was 1369 mL (95% CI 601–2137) more positive in the Na154 arm ($p < 0.001$), despite comparable non-study fluid sources. Hyponatremia < 135 mmol/L was encountered in four patients (11.8%) under Na54 compared to none under Na154 ($p = 0.04$), but there was no significantly more hyponatremia < 130 mmol/L (1 versus 0; $p = 0.31$). There was more hyperchloremia > 109 mmol/L under Na154 (24/35 patients, 68.6%) than under Na54 (4/34 patients, 11.8%) ($p < 0.001$). The treating clinicians discontinued the study due to clinical or radiographic fluid overload in six patients receiving Na154 compared to one patient under Na54 (excess risk 14.2%; 95% CI − 0.2–30.4%, $p = 0.05$).

Conclusions: In adult surgical patients, sodium-rich maintenance solutions were associated with a more positive cumulative fluid balance and hyperchloremia; hypotonic fluids were associated with mild and asymptomatic hyponatremia.

Keywords: Fluid overload, Maintenance fluid therapy, Hyperchloremia, Hyponatremia, Sodium, Chloride, Fluid balance

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Introduction

Maintenance fluid therapy is prescribed to cover hospitalized patients' daily needs for water and electrolytes when they are unable to ingest food or fluids [1, 2]. They are routinely used in the daily care of hospitalized patients around the world. Evidence shows maintenance fluids are a more important source of potentially harmful fluid and electrolyte administration than resuscitation fluids, whose detrimental effects have received much more scientific attention [3]. Maintenance fluid therapy should also be viewed separately from replacement solutions, which are used to substitute lost fluids or ongoing losses and need to contain as much sodium as the fluids lost [1, 2, 4].

For many years, guidelines have advised that maintenance solutions be hypotonic, reflecting dietary reference values, despite being based on low-quality evidence [4–6]. This view was later challenged, most convincingly in a large-scale pediatric trial pointing out the increased risk of hyponatremia under hypotonic maintenance fluid therapy [7]. Pediatric guidelines were subsequently adapted and even clinicians treating adult patients were soon called upon to change their practice accordingly, even in the absence of data in this population [8, 9]. The matter remains highly controversial, especially as the focus on hyponatremia detracts from the fact that also the choice of isotonic maintenance fluids comes at a price [10–12]. It has been shown that even healthy adults with a normal kidney function need several days to realign renal sodium excretion with an abruptly increased sodium intake, causing fluid retention and body weight gain [13–16]. The perioperative gain of 2–3 kg of body weight due to positive salt and water balance has been associated with detrimental effects and also in critically ill adult (and pediatric) patients a positive cumulative fluid balance is a risk factor for morbidity and mortality [17–20].

We designed the Tonicity Of Perioperative MAintenance SoluTions trial (TOPMAST) to test the hypothesis that maintenance fluid therapy containing 154 mmol per liter of sodium (as in the ubiquitous NaCl 0.9%) compared to 54 mmol per liter leads to increased fluid retention in adult patients undergoing major surgery. We also sought to evaluate different specific potential harms: the occurrence of sodium and chloride disturbances, renal injury and fluid-related clinical adverse events. Finally, we aimed to explore the study fluids' physiological behavior by measuring markers of volume status and capillary leakage.

Materials and methods
Trial design and patients
We performed this double-blind, randomized controlled trial at the tertiary care Antwerp University Hospital

Take-home messages

Isotonic maintenance solutions cause an importantly more positive cumulative fluid balance and substantial hyperchloremia revealing them as an independent cause of potentially detrimental fluid sodium and chloride overload, problems which have mainly been accredited to resuscitation fluids to date.
In adult patients undergoing major surgery, hyponatremia is encountered more frequently under maintenance therapy containing 54 mmol per liter of sodium but it is mostly mild and asymptomatic.

(Belgium). Our ICU is a 45-bed mixed ICU that receives medical and surgical patients and offers all types of organ support. The study was approved by the hospital's Institutional Review Board (reference number 17/04/034). The trial was registered at ClinicalTrials.gov (NCT03080831) and its protocol pre-published [21]. Eligible patients (at least 18 years of age) were to be scheduled for elective thoracic surgery: pulmonary (bi)lobectomy, segmentectomy, wedge or sleeve resections, by means of thoracotomy or video-assisted or robot-assisted thoracoscopy. Patients undergoing pneumonectomy were not eligible for the study due to a restrictive fluid policy in our institution.

Patients were excluded using two sets of exclusion criteria: (1) clinical situations that would render the primary endpoint difficult to interpret: an estimated glomerular filtration rate lower than 60 ml/min/1.73 m^2 (CKD-EPI) [22]; a body mass index below 15 kg/m^2 or exceeding 40 kg/m^2; chronic diuretic or desmopressin use; liver failure; pregnancy; treatment with (par)enteral feeding. Patients could also be excluded from the analysis of the primary endpoint only when acute kidney injury was encountered since this would render the effect size less interpretable in the majority of patients with a normal kidney function; (2) potential patient harm by the study fluids: severe heart failure; brittle diabetes mellitus; neurological contra-indications; the syndrome of inappropriate secretion of antidiuretic hormone; preoperative electrolyte disorders, including a sodium level below 130 mmol/L or over 150 mmol/L or a potassium level over 5 mmol/L.

Randomization and masking
Patients were randomly allocated (1:1) to receive one of the two different study fluids, both containing glucose as recommended by guidelines [4]. Na154 was NaCl 0.9% in glucose 5% with an added, guideline-recommended dose of 40 mmol/L of potassium chloride (KCl) [4]. Although potassium has a negligible effect on tonicity after administration, this addition essentially renders this solution slightly hypertonic. Yet, the treatment was deemed a real-life comparator, as NaCl 0.9% remains by far the

most widely used fluid worldwide and is frequently used as maintenance solution. Potassium chloride is the most common concentrated electrolyte solution to administer the necessary potassium [23]. Na54 was a premixed solution (Glucion 5%®, Baxter Healthcare, Deerfield Illinois, USA) containing sodium 0.32% (54 mmol/L) in glucose 5%, potassium (26 mmol/L), chloride (55 mmol/L), phosphate (6.2 mmol/L), magnesium (2.6 mmol/L), and lactate (25 mmol/L).

Treatment allocation was concealed from study investigators, caretakers and patients, and was performed by a collaborator independent of the study. Solutions were batch-prepared using opaque bags that were identical in appearance. To ensure maximal blinding, each treatment was randomly assigned twice to the labels A to D. Randomization was stratified by body weight (lower or higher than 74 kg, based on the median of a historical cohort), as this was an important determinant of the amount of study fluid to be administered. The randomization schedule was electronically generated using permuted block randomization with a block size of four and concealed in consecutively numbered sealed opaque envelopes that were opened after patient recruitment.

Procedures

The day before surgery, potential subjects were informed of the study by a member of the study team. Upon agreement, they provided written informed consent and were randomized. Shortly after the induction of general anesthesia, the bladder was voided and the study fluid was initiated at a guideline-recommended rate of 27 mL per kg of body weight per day with a maximum of 100 mL per hour [4]. The administration rate remained unchanged during surgery and in the ICU until the end of the study was reached as soon as any of the following situations occurred: the patient was discharged from the ICU, an adverse event occurred for which the treating physician decided the study treatment needed to be stopped, or the time reached 8 A.M. on the third postoperative day if the patient was still in the ICU. The detailed study outline is reported in Online Appendix [21]. As the use of diuretics would render the interpretation of the primary and secondary endpoints impossible, clinicians were asked to use diuretics only in the case of clinically relevant fluid overload, to stop the study at that time and to report this as an adverse event. All adverse events were monitored closely. On the case report form, specific attention was given to predefined adverse events that could be related to the study treatment: clinical or radiographic occurrence of fluid overload, hyperkalemia > 5 mmol/L, and evolving hyponatremia < 130 mmol/L with or without symptoms. As the treatment of sodium and potassium

disorders depends on the baseline value, the speed of increase or decrease and the clinical picture, the approach to electrolyte disorders and the (dis)continuation of the study treatment remained at the discretion of the treating clinicians.

During the entire treatment period, all urine was collected using a bladder catheter. Resuscitation fluids and blood products were administered at the discretion of the treating clinicians and were recorded. Oral fluid intake, perioperative blood loss and drain outputs were also assessed to calculate net cumulative fluid balance. Sodium (post hoc albumin-corrected [24, 25], see Online Appendix), chloride, potassium, creatinine, albumin and aldosterone were sampled at fixed time points: at the start and the end of surgery, upon ICU admission, each morning and evening in the ICU, and at the end of the study. Neutrophil gelatinase-associated lipocalin (NGAL) was assessed later as an exploratory analysis. Body weight was not measured as this was deemed too error prone and influenced by weight loss due to reduced caloric intake.

Outcomes

The primary endpoint of the study was net cumulative fluid balance, calculated as the sum of all intravenous fluids (study fluid, resuscitation fluids, transfusions) and oral fluid intake minus urinary output, perioperative blood loss and drain outputs. The following secondary endpoints were selected: the occurrence of hyponatremia (serum sodium below the lower limit of the normal range (135 mmol/L) with a decrease of at least 3 mmol/L from the preoperative measurement, to account for laboratory measurement errors in already slightly hyponatremic patients, analogous to the pediatric landmark study [7]); hyponatremia (< 130 mmol/L); hypernatremia (> 145 mmol/L); hypernatremia (> 150 mmol/L); hyperchloremia (> 109 mmol/L); and hypochloremia (< 101 mmol/L). We also considered the difference from the baseline value of sodium and chloride and their differences between the two treatment arms, and did the same for creatinine and NGAL, a sensitive early marker of renal tubular damage [26, 27]. As safety outcomes, we assessed the occurrence of acute kidney injury defined as creatinine-based AKIN stage 1 or higher, new-onset atrial fibrillation and the lowest PaO_2/FiO_2 ratio after ICU admission [28]. We also considered the number of times the study was halted because of the predefined adverse events (see "Procedures"). As exploratory outcomes, we assessed the physiological behavior of both solutions by measuring aldosterone as a marker of hypovolemia-induced activation of the renin–angiotensin–aldosterone system, and serum albumin levels as a marker of capillary leakage.

Sample size and statistical analysis

Statistical analyses were performed using Stata 14 (Stata-Corp LP, Texas, USA). All analyses were conducted on an intention-to-treat basis. Statistical significance was set at a p value of less than 0.05 (two sided) for all tests. For the primary outcome, a mixed effects model was fitted with net cumulative fluid balance as the outcome parameter, treatment, time (as repeated measure), their interaction as fixed effects and time as a random slope for each subject. To adjust for post-randomization imbalances between treatment groups, the primary endpoint analysis was adjusted for cumulative amounts of resuscitation fluids, oral fluid intake and blood loss/drain output (as fixed effects). As a sensitivity analysis for Online Appendix, the model was refitted by adding the quadratic term of time and its interaction with treatment to assess the appropriateness of assuming a linear relationship of the outcome over time. Other sensitivity analyses of the primary endpoint, reported in Online Appendix, included the patients that developed AKI or adjusted for baseline imbalances.

The differences in serum values (sodium, chloride, creatinine, NGAL, aldosterone and albumin) between the two solutions were assessed using random intercept models which included treatment and time (categorical) as fixed effects, the baseline value as covariate and all subsequent values as outcomes. Secondary and safety outcomes for each group were reported as percentages with nominal p values for comparisons between groups (using Chi^2 or $N-1Chi^2$ as appropriate) [29]. The iterative method of Miettinen and Nurminen was used to construct the 95% confidence intervals for the between-treatment differences in the proportions of patients developing adverse events [30].

The sample size estimation was based on the results of our experiment in healthy volunteers [16]. We determined, using an independent means t test, that a sample size of 68 patients would provide a power of 80% to detect a difference in fluid balance of 678 mL with a standard deviation (SD) of 927 mL after 48 h with an alpha set at 0.05 and assuming a 10% dropout rate.

Results

From March 2017 to July 2018, 110 patients were screened by the study team, of whom 29 patients were excluded, in most cases ($n=27$) due to the subset of exclusion criteria regarding the interpretability of the primary endpoint. Eleven patients refused content, therefore, 70 patients were eventually randomized (Fig. 1). All patients had a renal sequential organ failure assessment (SOFA) score of 0 at baseline. No patient had sepsis at the time of randomization. One patient in the Na54 arm was randomized but failed to undergo the study treatment or any of the investigations related to the study. All patients received their intended treatment. In each treatment group, one patient developed acute kidney injury, and—as predefined in the protocol—was excluded from the analysis of the primary endpoint (see Online Appendix for sensitivity analysis that included these patients). The study stopped recruitment after the final stratum included the necessary numbers. The patients' characteristics and details of their fluid therapies are presented in Table 1. Off-study fluid balance, potentially the most important confounder of fluid balance if incompletely leveled down by randomization, was very comparable under both treatments, and there was no significant difference in any of its individual components, blood loss, drain outputs, oral intake, or—most importantly—resuscitation fluids during and after surgery (Table 1).

Primary outcome

The effect of treatment on net cumulative fluid balance is shown in Fig. 2. The estimated fluid balance at 72 h was significantly more positive in the Na154 arm (4490 mL; 95% CI 3925–5054) than in the Na54 arm (3120 mL; 95% CI 2580–3661), a difference of 1369 mL (95% CI 601–2137; $p < 0.001$). Predicted values of fluid balance at each 12 h time point are reported in Online Appendix. The effect was even more pronounced in the sensitivity analysis including a quadratic term in time, reported in Online Appendix. At 72 h, a mean volume of 6.2 L of study fluid would have theoretically been administered (calculated by multiplying the entire cohort's mean body weight of 76.6 kg by the fixed rate of 27 mL/kg/day). The composition of the study solution was thus responsible for an additional fluid retention of 22% (95% CI 10–34%) of its infused volume.

Secondary outcomes (electrolyte disturbances) and effect on electrolyte levels over time

The impact of each solution on electrolyte levels over time and on the occurrence of electrolyte disturbances is summarized in Fig. 3 and Table 2. 4/34 patients developed hyponatremia (< 135 mmol/L) in the Na54 group versus zero patients in the Na154 group (excess risk 11.8%, 95% CI 1.1–26.8%, $p = 0.04$). Of the former, only one patient developed hyponatremia below < 130 mmol/L. 3/35 (8.6%) patients developed hypernatremia in the Na154 arm versus zero patients under Na54 ($p = 0.08$). Hyperchloremia was significantly more frequent under Na154 and was encountered in 24/35 patients (68.6%) of cases compared to 4/34 (11.8%) under Na54, an excess risk of 56.8% (95% CI 35.3–72.8%, $p < 0.001$).

Safety outcomes

From a clinical perspective, the study was never halted due to adverse events related to evolving or symptomatic hyponatremia (Table 2). On the other hand, the treating

Fig. 1 Cohort derivation plot
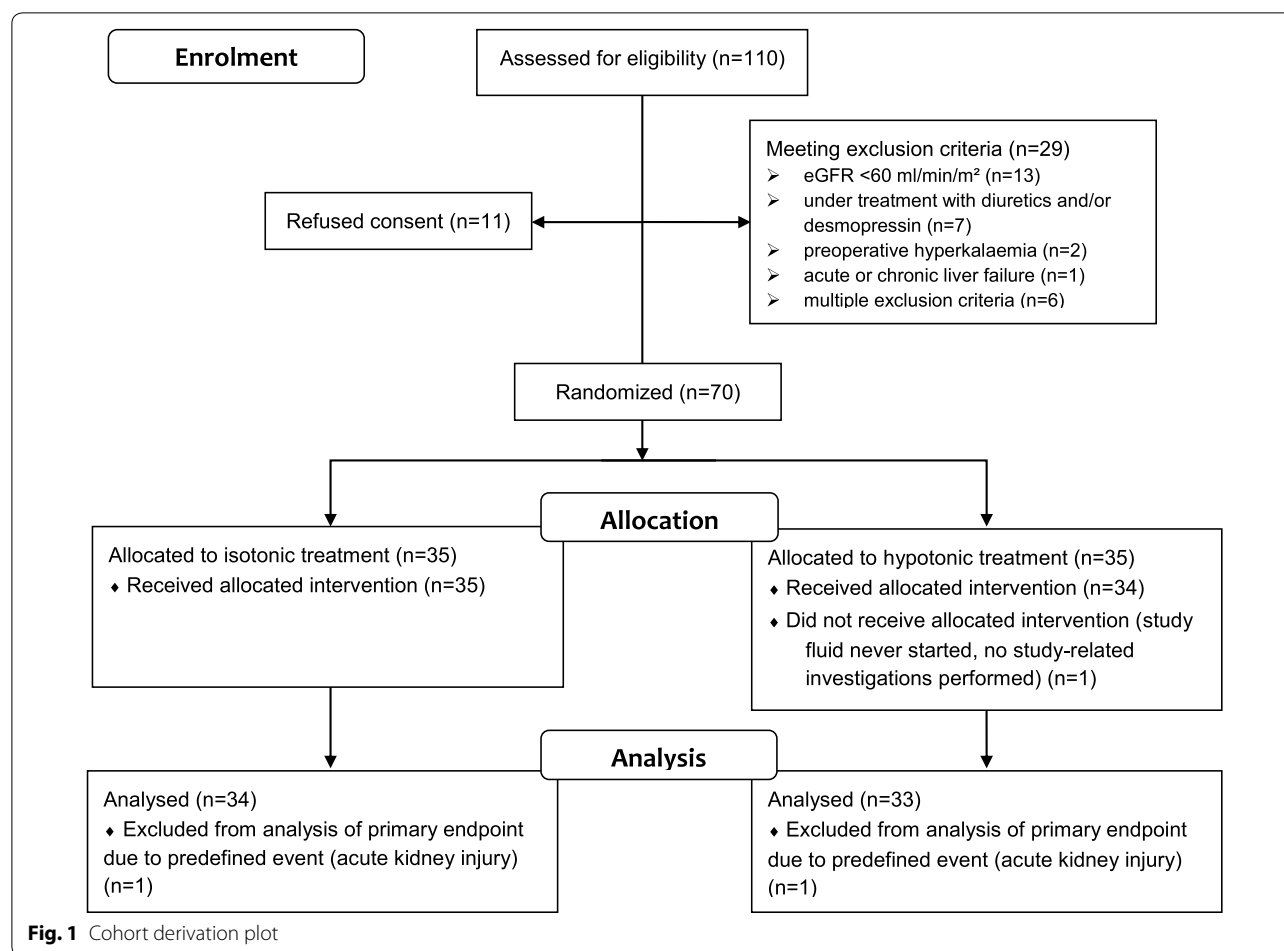
clinicians ended the study treatment in 6/35 patients (17.1%) due to clinical or radiographic pulmonary fluid overload under Na154 treatment versus 1/34 patient in the Na54 arm (excess risk 14.2%; 95% CI − 0.2–30.4%, $p = 0.05$). All these instances were registered as serious adverse events (Table 2 and Online Appendix) and diuretics—that were not used otherwise at any time during the study—were administered to all these patients immediately after the termination of the study period. One patient in each group developed acute kidney injury AKIN stage 1. There was no significant difference in creatinine levels, but serum NGAL was significantly higher in the Na154 arm ($p < 0.001$) (Fig. 3). No patients needed renal replacement therapy. Only one patient (Na54 group) died during his hospital stay (for details, see Online Appendix). This event was deemed unrelated to the study.

Exploratory outcomes

Aldosterone levels, not significantly different between the treatments, only showed a significant increase compared to baseline at the end of surgery. Almost all patients in both arms rapidly developed severe hypoalbuminemia.

Discussion

Effects on fluid balance

Our findings show that adult patients who undergo major thoracic surgery develop a markedly more positive net cumulative fluid balance under correctly dosed maintenance fluid therapy with a solution containing 154 mmol per liter of sodium than using a solution with 54 mmol per liter. These results suggest that the sodium content of intravenous maintenance fluids rather than their volume per se is a relevant contributor to the well-known problem of fluid overload [2, 31]. The scarce previous studies made it difficult to distinguish the effects of volume and sodium on fluid retention, as they combined both aspects in one intervention [17, 32]. Although our study was not powered to assess the clinical impact of a disturbed fluid balance, the finding that Na154 imposed an almost statistically significant 14.2% excess risk of hypervolemia-related respiratory adverse events for which the

Table 1 Baseline and study treatment characteristics

	Na54 (*n* = 34)	Na154 (*n* = 35)	*p* value
Patient characteristics			
Age (years)	62.7 (9.0)	62.2 (7.2)	0.80
Sex (% female)	12 (35.3)	7 (20.0)	0.16
Body weight (kg)	75.6 (13.1)	77.7 (14.9)	0.53
Body mass index (kg/m^2)	25.7 (4.7)	25.8 (4.3)	0.95
Baseline creatinine (mg/dL)	0.76 (0.16)	0.78 (0.14)	0.62
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2)	104 (20.9)	107 (26.3)	0.60
Characteristics of surgeries			
Type of surgery			
(Bi)lobectomy	24 (70.6)	26 (74.3)	0.75
Wedge resection/segmentectomy	9 (26.5)	7 (20.0)	0.75
Other	1 (2.9)	2 (5.7)	0.75
Surgical approach			
Thoracotomy	19 (55.9)	21 (60.0)	0.93
Robot-assisted thoracic surgery (RATS)	10 (29.4)	9 (25.7)	0.93
Video-assisted thoracic surgery (VATS)	5 (14.7)	5 (14.3)	0.93
Lung cancer as the reason for surgery	33 (97)[a]	34 (97)[b]	1.00
Use of patient-controlled epidural analgesia (PCEA)	33 (97.1)	29 (82.9)	0.11
Duration of surgery (hours)	3.1 (2.4–3.6)	3.8 (2.7–4.3)	0.04
Duration of mechanical ventilation (hours)[c]	4.1 (3.6–4.8)	4.8 (4.0–5.4)	0.07
Volume of intraoperative resuscitation fluids (mL)	1500 (1000–2000)	1500 (1000–2250)	0.74
Dose of intraoperative noradrenaline (mcg)	491 (162–906)	778 (184–1949)	0.09
Study period characteristics			
Mean duration of study treatment (hours)	39.3 (15.5)	38.5 (16.7)	0.44
Median duration of study treatment (hours)	29.5 (26.7–50.3)	29.3 (25.3–48.1)	0.44
Cumulative volume of blood loss and drain outputs (mL)	795 (450–1060)	890 (450–1940)	0.24
Cumulative urine output (mL)	2178 (1460–3100)	1945 (1290–3890)	0.33
Cumulative volume of administered study fluid (mL)	2772 (2159–4252)	2619 (2048–4286)	0.76
Cumulative volume of postoperative resuscitation fluids (mL)	0 (0–1000)	0 (0–500)	0.49
Cumulative volume of oral fluid intake (mL)	400 (5–925)	600 (200–1325)	0.11
Cumulative off-study fluid balance (mL)	1508 (890–2175)	1425 (1020–2200)	0.93

p values are for between-group differences in baseline characteristics, determined by independent means *t* test, Fisher's exact test or Mann–Whitney *U* test as appropriate. Data are mean (SD), *n* (%) or median (IQR). Off-study fluid balance is calculated as the difference between the all non-study fluid intake (resuscitation fluids during and after surgery and oral intake) and output (blood loss and drain outputs)

[a] One patient underwent surgery for vascular anomaly; one patient eventually turned out to have no lung cancer but aspergilloma on the resection specimen

[b] One patient underwent bullectomy

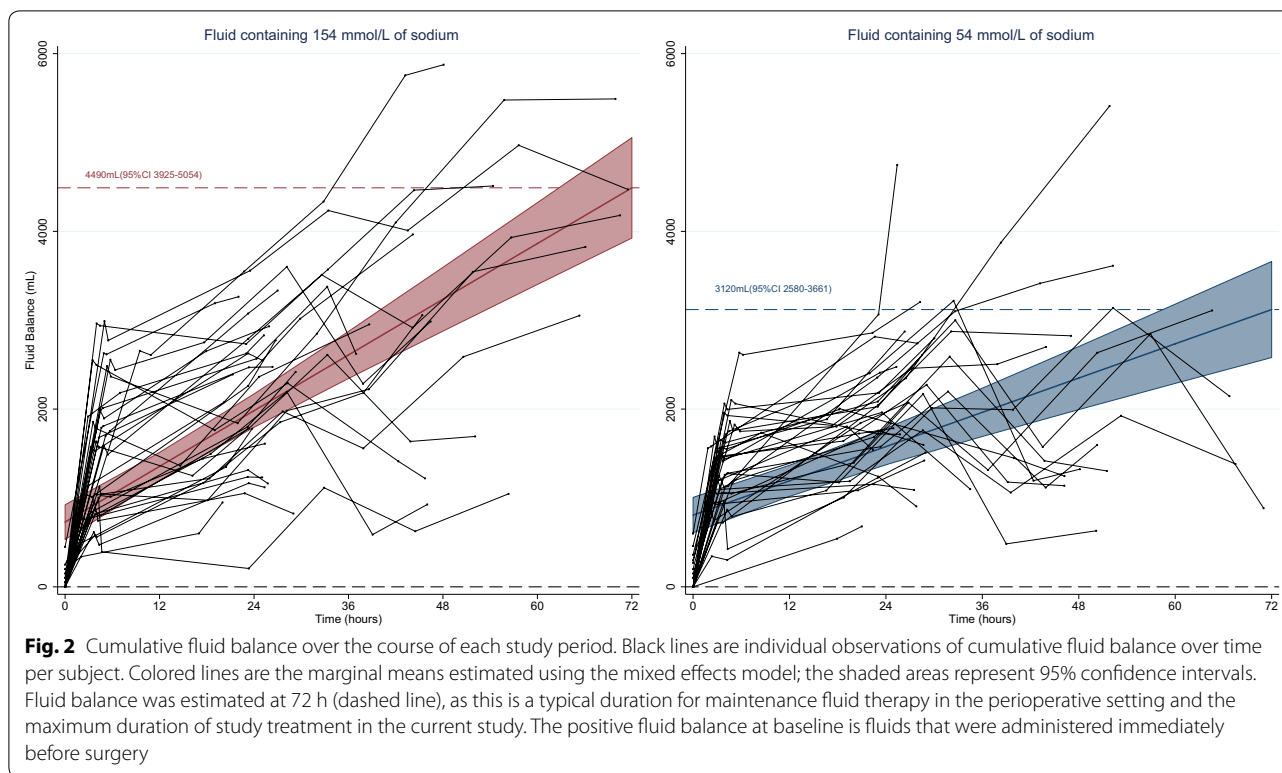[c] All patients were extubated in the operating theater

study had to be halted provides a clear safety signal that deserves our closest attention. This issue also deserves clarification in future dedicated pediatric research, especially since the association between a positive fluid balance and substantial morbidity was recently confirmed in critically ill children [19].

The underlying physiological rationale, the temporary malalignment of an abruptly increased sodium intake and its excretion by even perfectly healthy kidneys, has been elucidated in older and recent experiments, but the effect size in a clinical setting remained unknown to date [13–16]. For decades, healthy adults have been urged to limit their daily sodium intake to 2.3 g. One liter of NaCl 0.9%, while providing less than half of the recommended daily water intake, contains 3.5 g of sodium. Ringer's lactate and other so-called balanced solutions are common isotonic maintenance alternatives but still contain 3–3.2 g of sodium per liter and thus will not prevent the problem concerned.

Effects on sodium

The only justification for isotonic maintenance fluid therapy is the risk of potentially clinically important hyponatremia induced by hypotonic fluids. This was the

Fig. 2 Cumulative fluid balance over the course of each study period. Black lines are individual observations of cumulative fluid balance over time per subject. Colored lines are the marginal means estimated using the mixed effects model; the shaded areas represent 95% confidence intervals. Fluid balance was estimated at 72 h (dashed line), as this is a typical duration for maintenance fluid therapy in the perioperative setting and the maximum duration of study treatment in the current study. The positive fluid balance at baseline is fluids that were administered immediately before surgery

main trigger to the recent paradigm shift in pediatric patients [9]. As found in the secondary outcomes of our study, there was indeed a significant difference between serum sodium levels under both treatments and a higher number of patients developing sodium levels below 135 mmol/L. On the other hand, hyponatremia below the much more clinically relevant threshold of 130 mmol/L was observed in only one patient who was also unexpectedly treated with desmopressin during the study [33]. Moreover, the study was never halted by the treating clinicians due to the clinical symptoms of hyponatremia. It, therefore, appears that adults do not develop the same clinical problems as observed in children [7].

Effects on chloride

Hyperchloremia and chloride administration are increasingly believed to be harmful [34–38]. In our study, where it was a secondary outcome, it was encountered in most patients in the Na154 arm and must have been aggravated by the very common clinical practice of providing the daily potassium needs as a concentrated KCl solution. Since all resuscitation crystalloids used during the study contained only 98 mmol/L of chloride, we confirm our previous finding that a chloride-poor resuscitation strategy alone does not protect patients from hyperchloremia if maintenance solutions and additional electrolytes are

ill-considered [3]. Balanced solutions are preferred by many clinicians as their resuscitation, replacement and maintenance fluids of choice to reduce chloride burden. It is easily overlooked that adequately supplementing these solutions with KCl according to guidelines brings their chloride content near the level of that of NaCl 0.9% [4].

Effects on kidney function, volume status and fluid distribution

Although there was no difference in kidney function assessed by the AKIN criteria, the sensitivity of creatinine is hindered by its delayed increase. Serum NGAL, an early marker of renal tubular damage, was significantly higher under Na154. Although the clinical importance remains unproven, this alarming finding deserves further study, especially since the study was underpowered to detect clinically overt renal damage. It is also unclear whether Na154's tonicity, the ensuing fluid retention or its chloride content is the culprit.

In healthy volunteers, isotonic maintenance fluids cause (unintentional) plasma expansion [16]. In the current clinical setting, in which patients could still have been hypovolemic, fluid retention due to Na154 could thus have had the potential to improve
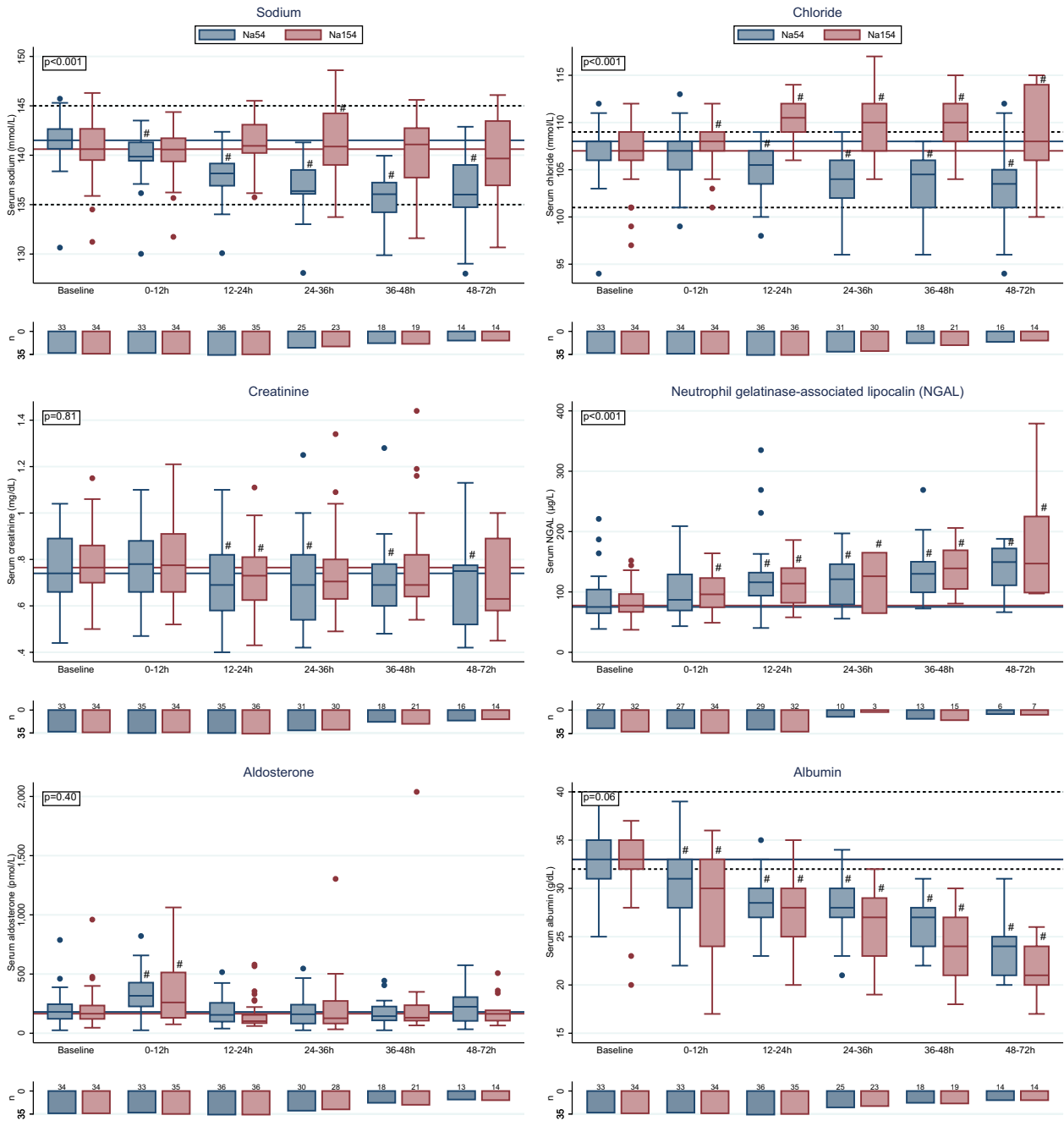
Fig. 3 Serum levels of electrolytes (sodium and chloride), markers of kidney function (creatinine) and kidney injury (NGAL), and markers of hypovolemia-induced activation of the renin–angiotensin–aldosterone system (aldosterone) and capillary leakage (albumin) over the course of the treatment periods. In-graph *p* values are for the difference between the two fluids using random intercept models with treatment and time (categorical) as fixed effects, the baseline value as covariate and all subsequent values as outcomes. Colored lines resemble the median value at baseline for each fluid. Black dashed lines represent the electrolytes' normal range. # indicates significantly different from baseline at a fluid-specific level (*p* < 0.05, Holm-adjusted to correct for multiple testing). *n* can be higher than the number of randomized patients when two measurements happened in one patient within the same 12-h time frame

Table 2 Secondary and safety outcomes

	Na54 (*n* = 34)	Na154 (*n* = 35)	*p* value
Secondary outcomes: electrolyte disturbances			
Sodium			
Hyponatremia (< 135 mmol/L)	4 (11.8)	0 (0)	0.04
Hyponatremia (< 130 mmol/L)	1 (2.94)	0 (0)	0.31
Hypernatremia (> 145 mmol/L)	0 (0)	3 (8.6)	0.08
Hypernatremia (> 150 mmol/L)	0 (0)	0 (0)	
Chloride			
Hypochloremia (< 101 mmol/L)	6 (17.6)	0 (0)	0.01
Hyperchloremia (> 109 mmol/L)	4 (11.8)	24 (68.6)	< 0.001
Safety outcomes			
Clinical outcomes			
Acute kidney injury (AKIN stage 1 or higher)	1 (2.9)	1 (2.9)	0.98
Need for renal replacement therapy	0 (0)	0 (0)	
Lowest paO_2/FiO_2 ratio after ICU admission	356 (269–390)	334 (255–383)	0.55
New-onset atrial fibrillation	1 (2.9)	4 (11.4)	0.17
Predefined (serious) adverse events leading to the termination of study period by the treating clinicians			
Clinical or radiographic fluid overload	1 (2.9)	6 (17.1)	0.05
Evolving or symptomatic hyponatremia	0 (0)	0 (0)	
Hyperkalemia	0 (0)	1 (2.9)	0.32
Other (serious) adverse events	1 (2.9)[a]	0 (0)	0.31
Hospital mortality	1 (2.9)	0 (0)	0.31

Data on lowest PO_2/FiO_2 ratios are median (IQR); all other data are *n* (%). Number of electrolyte disturbances is the number of patients with at least one event. Detailed descriptions of serious adverse events can be found in Online Appendix

AKIN acute kidney injury network

[a] Study fluid stopped by the treating clinician when the patient developed hemorrhagic shock demanding massive transfusion

hemodynamic status. Administering hypotonic fluids to patients with (occult) hypovolemia is presumably the most important cause of hyponatremia because of the intensified secretion of antidiuretic hormone [12]. As our exploratory analysis showed that aldosterone levels did not differ significantly between both treatments, we conclude that Na154 does not lead to a more optimal volume status. The marked decline in albumin level suggests that, instead of improving volume status, intravascular fluid—including the additionally retained portion of Na154—rapidly leaked into the interstitial space due to a damaged endothelial glycocalyx [39]. We hypothesize this is the reason that aldosterone did not decrease under Na154, as was the case in healthy volunteers [16].

Limitations

Our study has certain limitations. For reasons of sample size, we opted to run the trial without a true clinical primary endpoint and with a delineated, homogeneous study population undergoing similar major surgical procedures. Second, although we assume our findings could be generalizable to more heterogeneous surgical populations and even critically ill patients, this remains to be proven in larger trials. Third, this was a pragmatic trial where the study protocol did not try to protocolize or interfere with the usual care of our team of experienced intensivists. As such, no specific scales were used to assess the neurological impact of hyponatremia or guide its treatment, chest X-rays were not reviewed by multiple radiologists, volume status was not formally assessed using hemodynamic monitoring and sodium intake was not controlled in the postoperative diet. Fourth, our patients were permitted to drink as will. A median volume of 400 mL and 600 mL of oral intake was thus ingested in the Na54 and Na154 arms, respectively, which could mean that part of the maintenance fluid therapy was unnecessary from a volume point of view. On the other hand, the oral intake covered less than the cumulative drain output and it is unusual in clinical practice for maintenance fluid rates, commonly prescribed in the morning, to be adapted throughout the day based on oral intake. Finally, the study was not powered to find clinically important differences in secondary and safety outcomes. Although the study provided safety signals in both treatment arms, definitive proof should be sought after in larger trials.

Conclusions

In adult surgical patients undergoing major surgery, sodium-rich maintenance solutions were associated with a more positive cumulative fluid balance and hyperchloremia, whilst hypotonic fluids were associated with mild and asymptomatic hyponatremia.

Author details

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Author contributions

NVR designed the study with input from PJ, TVDW, PVS, WV and MM. NVR drafted the protocol, aided by SH, PJ, PVS, TVDW and ER, SH, KVV, BE, AW, JH, PVS and PL coordinated the study before and during surgery and collected data, IB and KD coordinated the study in the intensive care unit and collected data. ER and TVDW advised on the statistical analysis. AVC and WV advised on the physiological explanation behind the findings. NVR is the guarantor of the study and wrote the first draft of the manuscript with all authors contributing to revisions. All authors had full access to all of the data.

Compliance with ethical standards

Conflicts of interest

Dr Van Regenmortel and Dr Malbrain report speaker's fees from Baxter Healthcare Corporation. Dr Van Regenmortel was member of an advisory board on fluid therapy organized by Baxter (2017). Dr Malbrain is member of the medical advisory board of Getinge. Dr Van Regenmortel and Dr Malbrain are the chairmen and co-founders of the International Fluid Academy (IFA), a non-profit organization promoting education on fluid management and hemodynamic monitoring that received unrestricted educational grants from the industry (www.fluidacademy.org). The IFA is integrated within the not-for-profit charitable organization iMERiT, International Medical Education and Research Initiative, under Belgian law. The other authors have nothing to disclose.

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