BJA

British Journal of Anaesthesia, 120 (2): 274–283 (2018)

doi: 10.1016/j.bja.2017.11.088
Advance Access Publication Date: 2 December 2017
Clinical Practice

CLINICAL PRACTICE

Normal saline *versus* a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomised controlled study

C. A. Pfortmueller[1,*], G.-C. Funk[2], C. Reiterer[1], A. Schrott[3], O. Zotti[1], B. Kabon[1], E. Fleischmann[1] and G. Lindner[4]

[1]Clinic for Anaesthesiology, General Intensive Care Medicine and Pain Management, Medical University of Vienna, Vienna, Austria, [2]Department of Respiratory and Critical Care Medicine, Otto Wagner Hospital and Ludwig Boltzmann Institute for COPD and Respiratory Epidemiology, Sozialmedizinisches Zentrum Baumgartner Höhe, Vienna, Austria, [3]Statistical Consulting, Statistik Ambulanz, Leobendorf, Austria and [4]Department of General Internal Medicine & Emergency Medicine, Hirslanden Klinik im Park, Zurich, Switzerland

*Corresponding author. E-mail: cpfortmueller@gmail.com.

This article is accompanied by an editorial: Saline studies: How (not) to put nails in the coffin by Scheeren & Lühker, *Br J Anaesth* 2018:120:203-205, doi: 10.1016/j.bja.2017.11.089.

Abstract

Background: This double-blind randomised controlled trial investigated whether normal saline or a balanced crystalloid has distinct effects on vasopressor use in patients undergoing major abdominal surgery.
Methods: Patients received either normal saline 0.9% or an acetate-buffered crystalloid for intraoperative volume replacement in a goal-directed fashion. The primary outcome was need for vasopressors; the secondary outcomes were the total dose of catecholamines, total perioperative fluid, and unplanned intensive care admissions.
Results: This study was terminated early for safety reasons. A total of 60 out of the planned 240 patients were randomized. Thirty patients received normal saline and 30 patients received the balanced crystalloid, with a total volume of 3427 (2732–4130) ml and 3144 (1673–4926), respectively. The normal-saline group developed hyperchloraemic metabolic acidosis. More patients needed vasopressors for circulatory support in the normal-saline group compared with the buffered crystalloid group (97% *vs* 67%, respectively; P=0.033). The median weight and anaesthesia duration-adjusted dose of norepinephrine were 0.11 (0.00–0.45) ng kg^{-1} min^{-1} and 0.00 (0.00–0.00) kg^{-1} min^{-1} in the normal-saline and balanced-crystalloid groups, respectively (P=0.003). Cox regression revealed that the need for vasopressors was related to a high volume of administered fluid, normal-saline resuscitation, and lower mean arterial blood pressure. There was no difference between the groups in total perioperative fluid and unplanned intensive-care-unit admissions. Between-group differences in the duration of anaesthesia did not influence the necessity for a vasopressor.

Editorial decision: August 31, 2017; **Accepted:** August 31, 2017

Conclusions: Compared with patients receiving a balanced crystalloid, normal saline in patients undergoing major abdominal surgery was associated with an increased need for vasopressor support. This should be interpreted in view of the large volume of fluid resuscitation and the small sample size because of the preliminary termination of the study.
Clinical trial registration: EudraCT 2014-004867-19, NCT 02414555.

Keywords: fluid therapy; haemodynamics; surgical procedures; operative

Editor's key points

- The association of goal-directed fluid therapy with normal saline or a balanced crystalloid with perioperative vasopressor requirements is unclear.
- The findings suggest that 0.9% saline resuscitation is associated with a higher need for vasopressor therapy than a balanced crystalloid.
- This association should be interpreted with caution because of the relatively high volume of fluid resuscitation and the small sample size because of preliminary termination based on the metabolic acidosis rates in the saline group.

Infusion solutions are amongst the most frequently administered medications in hospitalized patients.[1] In recent years, there have been many changes in the field of perioperative fluid therapy, and more attention has been drawn to the unwanted side-effects of colloidal and crystalloid solutions.[1] The increasing doubt about the safety and efficiency of colloid solutes in patients undergoing major surgery[2–4] has led to the increased use of crystalloid solutes.[5–7]

Normal saline 0.9% is currently amongst the most commonly used crystalloids in clinical practice, and is the most frequent choice for volume replacement.[8–13] Despite its name, the composition of normal saline is far from physiological. Both sodium and chloride concentrations in normal saline estimate 154 mmol litre^{-1}, thereby exceeding normal physiological levels in the extracellular fluid.[12,14,15] Normal saline is associated with the development of metabolic acidosis, presumably as a consequence of hyperchloraemia and a resulting decrease in the ionic gap.[11,12,14,16] Moreover, normal saline has been linked to changes in renal function in healthy volunteers, and blood transfusions and mortality in patients undergoing abdominal surgery.[11,12,17] In contrast to normal saline, balanced crystalloids contain metabolisable anions, such as lactate or acetate, which maintain electrolyte neutrality and are less associated to metabolic acidosis, albeit they are metabolized to bicarbonate.[1,18]

A recent study on patients undergoing cadaveric kidney transplantation compared the effect of normal saline and an acetate-buffered balanced crystalloid on early graft function.[19] Patients given a balanced crystalloid for fluid resuscitation received significantly less catecholamines for cardiocirculatory support compared with patients receiving normal saline.[19] This led to the hypothesis that, in patients undergoing major surgery, the need for vasopressor support might also be influenced by the type of fluid used for perioperative fluid therapy.

We, therefore, conducted a double-blind randomised controlled trial on patients undergoing major abdominal surgery, with the aim of clarifying whether a balanced crystalloid for perioperative fluid management is associated with less need for vasopressor support to maintain haemodynamic stability compared with normal saline.

Secondly, we investigated whether the use of a balanced crystalloid is associated with a lower incidence of metabolic acidosis and electrolyte disorders than with normal saline.

Methods

Study design and patient population

The study was approved by our local institutional review board (EK1877/2014), the Ethics Committee of the Medical University of Vienna, Austria, and registered in a clinical trial register (NCT02414555). Written informed consent was obtained from every patient included in the study.

We conducted a prospective, double-blind randomised controlled trial comparing the effects of normal saline and an acetate-buffered balanced-crystalloid solution on intraoperative haemodynamic stability in patients undergoing major abdominal surgery. The study was conducted between March 1, 2015 and February 29, 2016 at the Department of Anaesthesiology of the Medical University of Vienna, Austria.

The study included adult, non-pregnant patients who were scheduled for elective major abdominal surgery with an expected surgical duration of a minimum of 2 h. Major abdominal surgery included all gynaecological, urological, and general surgical operations requiring laparotomy. The exclusion criteria were as follows: severe cardiac dysfunction (left ventricular ejection fraction below 30% diagnosed by echocardiography) or chronic renal insufficiency [glomerular-filtration rate (GFR) below 30 ml min^{-1}], severe liver disease or chronic inflammatory disorders requiring long-term steroid therapy, signs of sepsis before the scheduled operation, critical illness in patients transferred from the intensive care unit (ICU) to the operating theatre, contraindications for oesophagus Doppler monitoring, and additional intraoperative epidural anaesthesia.

The study was terminated early for safety reasons after a discussion of the interim results with local authorities. The study was terminated after 60 of 240 planned patients.

Primary end point of the study

The primary end point of the study was catecholamine use to maintain the target mean arterial pressure (MAP). The secondary end points were the difference in dose of catecholamines required to maintain cardiovascular stability between groups, difference in volume required to maintain cardiovascular stability, and unplanned ICU transfers.

Randomisation

Computer-based randomisation was performed using blocks of 10 patients and sealed envelopes. At the time of transfer to the preoperative care unit of the Department of Anaesthesiology, the patients were randomized to either receive normal saline (theoretical osmolality 308 mOsmol kg^{-1}, potential base excess −24 mmol $litre^{-1}$, Na^{+} 154 mmol $litre^{-1}$, Cl^{-} 154 mmol $litre^{-1}$) or a chloride-reduced acetate-buffered balanced crystalloid (Elomel Isoton; Fresenius Kabi Austria GmbH, Graz, Austria; theoretical osmolality 302 mOsmol kg^{-1}, potential base excess 0 mmol $litre^{-1}$, Na^{+} 140 mmol $litre^{-1}$, Cl^{-} 108 mmol $litre^{-1}$, K^{+} 5 mmol $litre^{-1}$, Ca^{++} 2.5 mmol $litre^{-1}$, Mg^{++} 1.5 mmol $litre^{-1}$, and acetate 45 mmol $litre^{-1}$). No i.v. fluid was administered prior to this point. The blinded infusion fluid was given to the anaesthesiologist before the induction of anaesthesia.

Study conduct and anaesthesia

The patients included in the study received standard monitoring for major abdominal surgery (oxygen saturation, heart rate, invasive arterial blood pressure, electrocardiography, temperature, urine output, Narcotrend index, train-of-four monitoring, and central venous pressure).

The anaesthetic management was standardized. Propofol 2–3 mg kg^{-1}, rocuronium 0.6 mg kg^{-1}, and fentanyl 2–3 μg kg^{-1} were used for induction. Anaesthesia was subsequently maintained with sevoflurane. The fractional inspiratory oxygen concentration was regulated according to clinical requirements. The sevoflurane administration was adjusted by the attending anaesthesiologists in accordance with the Narcotrend index. Additional fentanyl was administered according to the patient's requirements. Further, a neuromuscular blocking agent was given as necessary to maintain one to two mechanical twitches in response to supramaximal stimulation (train-of-four stimulation) of the ulnar nerve at the wrist. Ventilation was mechanically controlled to maintain end-tidal carbon-dioxide pressure near 35 mm Hg. The tidal volume was set between 8 and 10 ml kg^{-1} lean body weight, in order to keep the peak inspiratory pressure below 30 mm Hg, and a positive end expiratory pressure of 5 mm Hg or higher was administered according to the patient's requirements. The temperature was monitored, and normothermia (core temperature >36°C) was maintained with forced-air warming. During surgery, arterial blood gas samples were obtained at least hourly.

Haemodynamic management

The patients received either isotonic saline or Elomel Isoton, depending on randomization. The patients received an infusion rate of 2 ml kg^{-1} ideal body weight per hour as the baseline rate. When the viscera were exposed, the infusion rate for patients during surgery was set at 5 ml kg^{-1} ideal body weight per hour. The ideal body weight for fluid maintenance rate was calculated according to Robinson's formula:

Men: ideal body weight (in kilograms)=52 kg+1.9 kg for every 2.5 cm over 150 cm

Women: ideal body weight (in kilograms)=49 kg+1.7 kg for every 2.5 cm over 150 cm

The designated target MAP was set according to preoperative values measured a day before the surgery on the surgical ward. The patients were divided into normotensive patients, with a systolic blood pressure (SBP) between 120 and 139 mm Hg or a diastolic blood pressure (DBP) between 80 and 89 mm Hg, and hypertensive patients with an SBP >140 mm Hg or a DBP higher than 90 mm Hg, as laid down by the World Health Organization.[20] Patients with an SBP lower than 120 were defined as 'hypotensive'. The intraoperative target MAP was set as follows: hypotensive group 60 mm Hg, normotensive group 70 mm Hg, and hypertensive group 80 mm Hg. If a patient fell below the designated target MAP, fluid therapy or vasopressor therapy was started according to a predefined algorithm for fluid resuscitation/vasopressor therapy, as described as follows.

For goal-directed fluid administration, oesophageal Doppler monitoring (CardioQ; Deltex Medical, Chichester, UK) was based on an algorithm recently published by the Anesthesia Working Group of the Enhanced Recovery after Surgery Society.[21] The haemodynamic parameters were continuously assessed during surgery.

Haemodynamic management was as follows: if the patient's MAP fell below the designated target MAP, stroke volume (SV) responsiveness was assessed by a volume challenge of 250 ml (fluid bolus). If there was a >10% increase in SV, but MAP was still below the designated target MAP, further fluid trials of 250 ml each were performed, up to the point where the patient no longer responded with a >10% increase in SV after the fluid bolus, or the patient's MAP was above the designated target MAP. If the SV increased <10% with the fluid bolus and the MAP was below the designated target MAP, a bolus of phenylephrine 0.1–0.2 μg was given to achieve a blood pressure above the designated target MAP. Phenylephrine was dosed up to a maximum dose of 0.8 μg phenylephrine per hour. If more than a total of 0.8 μg of phenylephrine in multiple boluses was necessary within 1 h, or the degree of hypotension was likely to require more than 0.8 μg phenylephrine per hour, continuous infusion of norepinephrine was started at a dose of 0.01–0.02 μg kg^{-1} min^{-1} and titrated to the designated target MAP by increments of 0.05–0.1 μg kg^{-1}. The indication to restart the fluid-bolus administration was a decrease in measured SV of >10% below the SV value recorded directly after the last fluid bolus. Norepinephrine was titrated down to the target MAP or stopped if fluid resuscitation alone resulted in a >10% increase in SV and the patients reached the designated target MAP.

Exit criteria

If the pH fell below 7.2, the bicarbonate fell below 14 mmol $litre^{-1}$, or the base excess was below −10 mmol $litre^{-1}$, and the reaction to catecholamines was insufficient (inability to hold target mean despite adequate catecholamine dosage in the absence of surgical complications, such as bleeding), the study fluid was switched to the acetate-buffered balanced crystalloid and the study was terminated.

Sample size calculation

Sample size calculation was based upon our previous study in patients undergoing renal transplantation using the primary target criterion, norepinephrine necessity.[19] Under the estimation that 15% of the patients in the balanced group need

norepinephrine *vs* 30% of the patients in the normal-saline group, a sample size of 120 patients per group was determined (5% α level and 80% power).

The study was terminated early for safety reasons after discussing the interim results with local authorities. Therefore, this study included 60 patients and not 240 patients as originally planned. After the early study termination, *post hoc* power was calculated and gave 67% power for vasopressor use and 90% power for catecholamines per kilogram body weight per minute of anaesthesia.

Statistical analysis

Statistical analysis was performed using STATA version 13.1 SE (StataCorp, College Station, TX, USA). Interval and ordinal variables are presented as medians with inter-quartile ranges (IQRs). Comparisons of interval and ordinal variables between the saline group and the acetate-buffered balanced-crystalloid group were performed using the Mann–Whitney *U* test. Comparisons of categorical variables between the saline group and the acetate-buffered balanced-crystalloid group were performed using Fisher's exact test. We applied the Bonferroni–Holm procedure to the outcome data in order to adjust for multiple testing.[22] In order to test whether the mean arterial blood pressure and laboratory values differed between the saline group and the acetate-buffered balanced-crystalloid group, we used a generalized estimating equation assuming normal probability distribution and a first-order exponential correlation matrix for repeated observations within one patient. In order to test for differences between the two study groups in the incidence of vasopressor administration, we used a log-rank test and a Kaplan–Meier failure plot for visualization. Logistic regression was used to exclude the effect of the duration of anaesthesia on our main outcome—vasopressor necessity. In order to test whether vasopressor use was preceded by hypotension, we used a Cox regression, including robust standard errors, with vasopressor use as the dependent variable, and mean arterial blood pressure and group allocation as the time-dependent predictor variables. For all analyses, the statistical significance was defined by a two-tailed $P<0.05$. Figures were drawn using GraphPad Prism 6.07 (GraphPad Software, La Jolla, California, USA).

Results

The study was terminated early for safety reasons after discussing the interim results with the study safety board and local authorities.

During the study period, a total of 60 patients were randomized and included in the study (see Fig. 1). Thirty patients

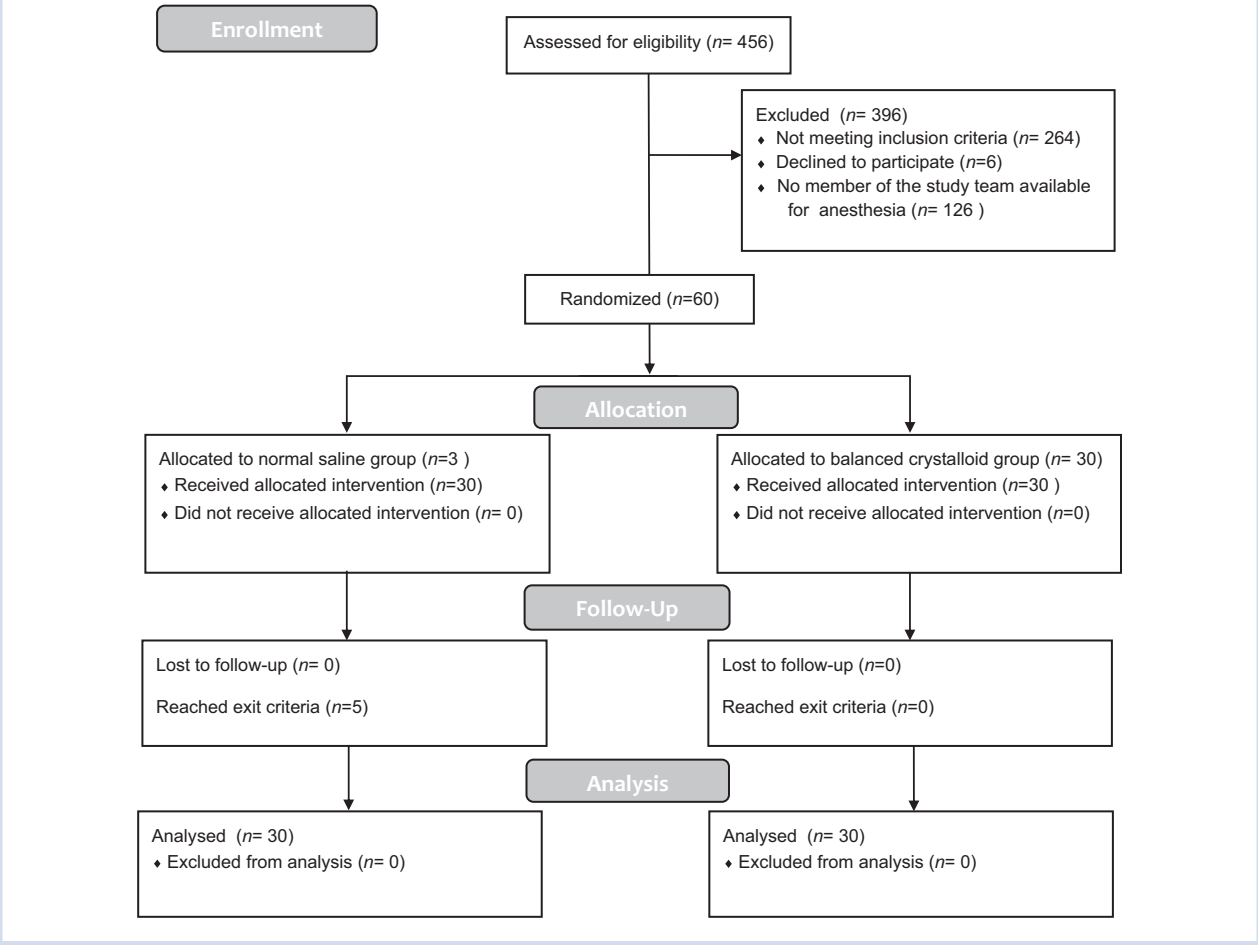

Fig 1. Consolidated Standards of Reporting Trials patient flow diagram.

Table 1 Patient data and baseline characteristics. GFR, glomerular-filtration rate

		Saline				Balanced solution					
		Count (%)	Median	Percentile 25	Percentile 75	Count (%)	Median	Percentile 25	Percentile 75	*P* Mann–Whitney	*P* Fisher
Sex	Male	13 (43)				11 (37)					0.79
	Female	17 (57)				19 (63)					
Age		30	58	43	67	30	63	50	69	0.19	
Height		30	171	165	175	30	170	163	175	0.8	
Weight		30	71	59	85	30	72	60	80	0.78	
Ideal body weight		30	63	59	70	30	63	58	71	0.98	
ASA	1	11 (37)				10 (33)					0.69
	2	16 (53)				16 (53)					
	3	3 (10)				4 (13)					
Prior history of hypertension	No	19 (63)				23 (77)					0.39
	Yes	11 (37)				7 (23)					
Preoperative creatinine (mg dl^{-1})		30	1.00	1.00	1.00	30	1.00	1.00	1.00	0.32	
Urea (mg dl^{-1})		30	10.5	8.0	18.0	30	14.0	11.0	16.0	0.27	
GFR (ml min^{-1}/1.73 m^2)		30	74	55	113	30	71	61	88	0.6	
Type of surgery	Bladder resection	0 (0)				2 (7)					0.63
	Colorectal resection	5 (17)				3 (10)					
	Hemihepatectomy	1 (3)				0 (0)					
	Hysterectomy	0 (0)				1 (3)					
	Intestinal reconstruction	1 (3)				3 (10)					
	Nephrectomy	3 (10)				1 (3)					
	Pancreatectomy	1 (3)				1 (3)					
	Radical prostatectomy	2 (7)				3 (10)					
	Small bowel resection	1 (3)				3 (10)					
	Tumour debulking (colorectal)	3 (10)				2 (7)					
	Tumour debulking (endometrium)	2 (7)				0 (0)					
	Tumour debulking (ovaries)	7 (23)				7 (23)					
	Tumour debulking (cervical)	4 (13)				4 (13)					

were randomised to normal saline and 30 patients to an acetate-buffered balanced crystalloid. The two groups were comparable in terms of age, sex, ASA classification, prior history of hypertension, preoperative renal function, and type of surgery (Table 1). The mean duration of anaesthesia was longer in the saline 0.9% group (317 min, IQR 275–369) than in the balanced group [234 min (162–318; P=0.004]. The exit criteria were reached in five patients (17%) in the saline 0.9% and zero patients (0%) in the balanced-infusate group (P=0.052). The intraoperative characteristics are presented in Table 2.

During surgery, patients in the saline 0.9% group received a median total of 3427 (IQR 2732–4130) ml of fluid *vs* 3144 (IQR 1673–4926) ml in the balanced-crystalloid group (P=0.19). Correction for duration of anaesthesia showed no difference between the groups in the total amount of fluid received (P=0.39).

Significantly more patients needed vasopressors for circulatory support during surgery in the group receiving normal saline compared with the balanced-crystalloid group (97% *vs* 67%; P=0.033). The median dose of norepinephrine adjusted for body weight and duration of anaesthesia was 0.11 (IQR 0.00–0.45) ng kg^{-1} min^{-1} in the normal-saline group and 0.00 (IQR 0.00–0.00) ng kg^{-1} min^{-1} in the balanced group (P=0.003).

The logistic-regression analysis for the primary outcome (i.e. vasopressor necessity) showed no association with duration of anaesthesia [odds ratio (OR) 0.996; 95% confidence interval 0.990–1.002; P=0.24), but a significant association with randomization to the saline group [OR 20.2 (2.2–188.9); P=0.009].

The Kaplan–Meier analysis showed that, with ongoing surgery, patients in the normal-saline group needed vasopressors more often than in the second group (Fig. 2; P=0.019). Cox analysis (Table 3) showed that the vasopressor requirement over time was significantly affected by the amount of fluid received, the randomization group, and the MAP.

The maximum chloride concentrations were higher in the saline group [115 (108–122) *vs* 108 (105–108) mmol litre^{-1}], as were variations in chloride during surgery [7 (2–16) *vs* 2 (0–9) mmol litre^{-1}] (P<0.0001). In the regression analysis, there was a trend towards hyperchloraemia in the normal-saline group compared with the balanced-crystalloid group (P<0.0001). Table 4 and Fig. 3 give an overview of the acid–base variables and electrolytes.

The base-excess minimum was lower in the normal-saline group than with the balanced-crystalloid regimen [−6.0 (−12 to +4) *vs* 0.0 (−5 to +3) mmol litre^{-1}; P<0.0001]. Furthermore, the change from start of surgery to base-excess minimum was higher in patients receiving normal saline. Fluctuations in serum sodium and potassium were similar between both groups (Table 4).

Table 2 Intraoperative data. Data are given as median (first to third quartile), unless otherwise indicated. BW, body weight

	Saline, n=30	Balanced solution, n=30	P Mann–Whitney U test	P Fisher's exact test	Bonferroni–Holm corrected α level	Significant difference between groups
Duration of anaesthesia (min)	317 (275–369)	234 (162–318)	0.004		0.0071	Yes
Total fluid (ml)	3427 (2732–4130)	3144 (1673–4926)	0.19		0.0167	No
Fluid per minute of anaesthesia (ml min^{-1})	11.3 (9.3–13.6)	12.0 (9.7–16.0)	0.39		0.05	No
Total blood loss	400 (200–600)	200 (50–500)	0.25		0.025	No
Exit criteria reached, n (%)	5 (17)	0 (0)		0.052	0.0125	No
Patients requiring vasopressors, n (%)	29 (97)	20 (67)		0.006	0.0083	Yes
Cumulative dose phenylephrine (μg kg^{-1} BW)	8.923 (5.263–15.200)	2.82 (0.00–13.25)	0.032		0.01	No
Cumulative dose norepinephrine kg^{-1} min^{-1} of anaesthesia (ng kg^{-1} BW min^{-1})	0.11 (0.00–0.45)	0.00 (0.00–0.00)	0.003		0.0063	Yes

Discussion

In this prospective, double-blind randomised controlled study, we compared the effects of normal saline and an acetate-buffered chloride-reduced crystalloid on the need for vasopressors for cardio-circulatory support in patients undergoing major abdominal surgery. After inclusion of a total of 60 patients, the study had to be ended for safety reasons, by the decision of the study safety board.

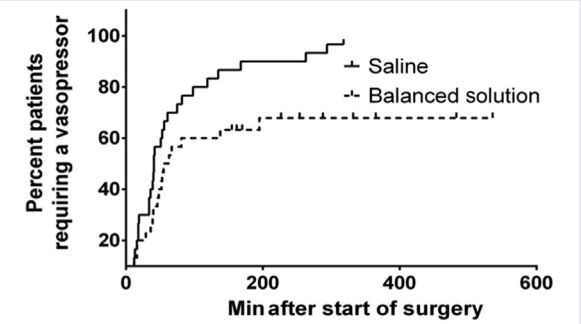

Fig 2. Kaplan–Meier analysis of vasopressor requirements over time (log-rank test: $P=0.0194$).

We found that normal saline for infusion in patients undergoing major abdominal surgery was associated with a significantly greater need for vasopressor support than with an acetate-buffered chloride-reduced crystalloid. It was also found that the absolute amount of vasoactive substances administered was significantly higher in patients receiving normal saline. Moreover, normal saline was associated with a constant increase in serum chloride concentrations over time and consequent hyperchloraemic acidosis, as expressed by a reduction in base excess over time.

To our knowledge, this is the first prospective randomised controlled study to investigate potential differences in haemodynamic stability between normal saline and a balanced-crystalloid infusion solution. The current findings are supported by previous experimental and clinical data.

The influence of perioperative fluid choice on vasopressor requirement was first described by Potura and colleagues.[19] Their study aimed to compare normal saline to an acetate-buffered crystalloid solute in terms of early graft dysfunction in patients after cadaveric renal transplantation; they detected a 50% decrease in catecholamine requirements in the balanced-crystalloid group.[19] An additional feature of our study was profound hyperchloraemia with an associated decrease in bicarbonate and base excess, and consecutive profound metabolic acidosis in the normal-saline group. This effect has also been described by other authors.[11,12,14,16,23–27] Only recently, large-scale studies and a meta-analysis showed that the use of chloride-rich infusion solutions may

Table 3 Cox-regression analysis of vasopressor requirements

Predictor variable	Hazard ratio with 95% confidence intervals	P-value
Fluid administered (ml min^{-1} of anaesthesia time)	1.01 (1.00–1.02)	0.001
Group allocation (1=saline; 2=balanced solution)	0.44 (0.24–0.79)	0.006
Mean arterial blood pressure (mm Hg)	0.97 (0.95–0.99)	0.027

Table 4 Electrolyte and acid–base data

	Saline					Balanced solution					P Mann–Whitney
	Median	Percentile 25	Percentile 75	Minimum	Maximum	Median	Percentile 25	Percentile 75	Minimum	Maximum	
Base-excess maximum	−1.0	−2.0	1.0	−11.0	4.0	1.5	0.0	2.0	−3.0	5.0	0.002
Base-excess minimum	−6.0	−9.0	−4.0	−12.0	4.0	0.0	−2.0	1.0	−5.0	3.0	<0.0001
Sodium minimum	138	137	139	134	143	138	136	139	128	142	0.34
Sodium maximum	141	139	142	136	146	139	138	141	129	144	0.028
Sodium variance	2	1	3	0	10	2	1	3	0	5	0.19
Chloride minimum	107	104	109	98	115	106	104	107	3	109	0.083
Chloride maximum	115	111	117	108	122	108	105	109	4	116	<0.0001
Chloride variance	7	6	9	2	16	2	1	3	0	9	<0.0001
Potassium minimum	4.00	3.00	4.00	3.00	5.00	4.00	4.00	4.00	3.00	4.00	0.25
Potassium maximum	4.00	4.00	4.00	4.00	5.00	4.00	4.00	4.00	3.00	6.00	0.058
Potassium variance	0.00	0.00	1.00	0.00	2.00	0.00	0.00	1.00	0.00	2.00	0.31
pH minimum	7.29	7.25	7.33	7.17	7.36	7.37	7.34	7.39	7.28	7.44	<0.0001
P_{CO2} minimum	36.0	32.4	38.5	28.2	43.6	34.9	33.0	38.8	27.5	43.0	0.87
P_{CO2} maximum	45.2	41.7	46.7	36.9	54.4	43.4	41.8	46.6	36.8	52.8	0.38
Base-excess minimum	19	17	21	15	22	24	23	25	18	27	<0.0001
Lactate maximum	0.9	0.7	1.1	0.5	4.7	1.0	0.8	1.4	0.5	2.4	0.4

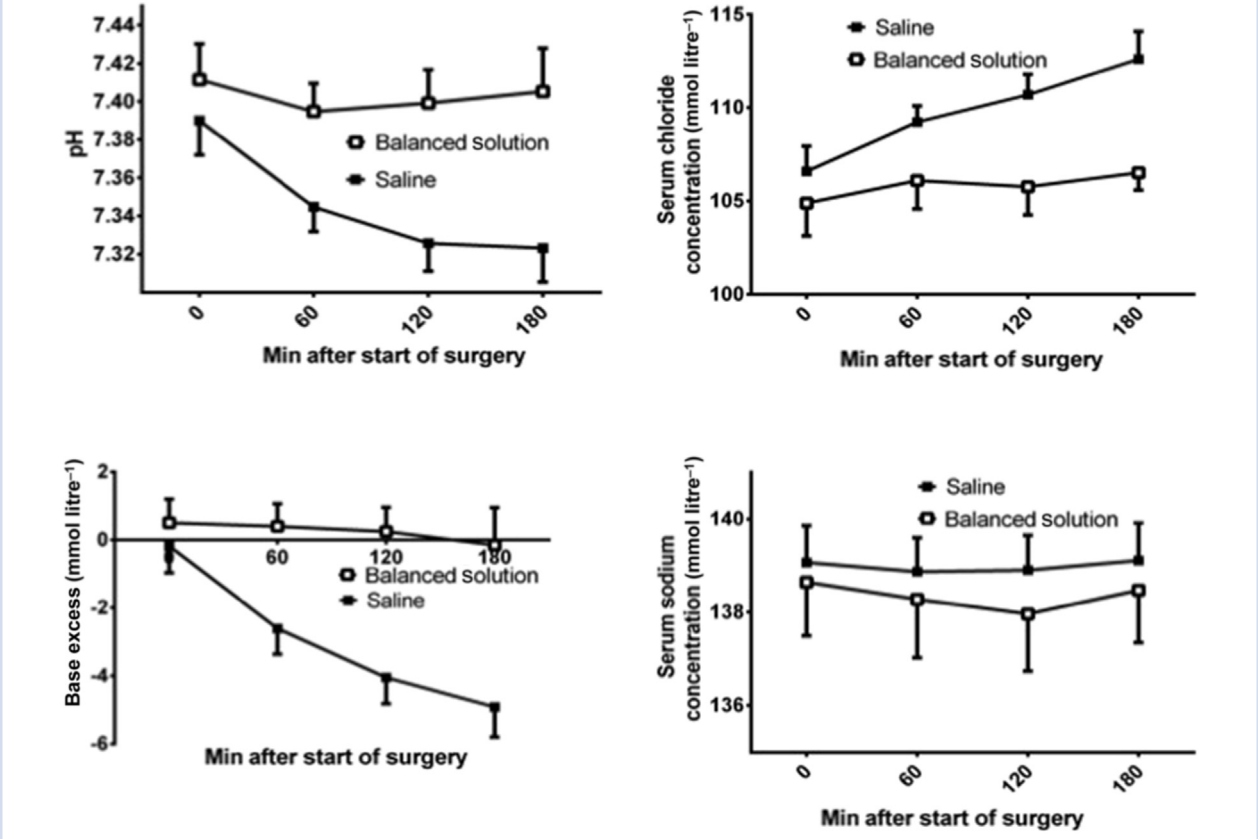

Fig 3. Electrolytes and acid–base changes over time.

be associated with adverse outcomes.[8,9,11] Given this evidence, together with other recent studies on this subject,[11,23,24] it seems plausible that hyperchloraemia, induced by infusion of normal saline, may be a direct trigger for unfavourable haemodynamic effects, as seen in our study.

Chloride homeostasis is mainly regulated by the kidneys, and is closely linked to bicarbonate and acid–base regulatory mechanisms.[28,29] The effect of hyperchloraemic solutions on the regulation of renal perfusion by plasma chloride in dogs was first shown in the 1980s in two studies conducted by Wilcox[30] and Wilcox and Peart.[31] After 30–45 min infusion of hypertonic chloride solutions renal vasoconstriction was detected, leading to a reduced GFR, whereas for sodium acetate the opposite was true, except that there was no increase in the renal filtration ratio.[30] In their crossover study on 12 healthy volunteers, Chowdhury and colleagues[17] showed that a colloid embedded in a balanced-crystalloid solution led to increased renal cortical tissue perfusion, whilst the same concentration of colloid embedded in saline 0.9% did not improve renal perfusion.[30,31] They also showed that, in comparison with a balanced crystalloid, the administration of 2 litres of normal saline to healthy volunteers was linked to a significant decline in renal-blood-flow velocity and renal cortical tissue perfusion.[17]

Kellum and colleagues[25] induced sepsis in adult rats, and treated them with either normal saline or lactated Ringer's solution. Renal perfusion diminished significantly with increasing hyperchloraemia and acidosis, and the MAP was markedly lower in the group receiving normal saline.[25] They also found that the MAP decreased in a dose-dependent manner in the saline 0.9% group, whilst hyperchloraemia and acidosis simultaneously increased.[25] Orbegozo and colleagues[32] compared normal saline with lactated Ringer's and Plasma-Lyte in rats with experimental sepsis. With normal saline, hyperchloraemic metabolic acidosis developed, followed by a time-dependent decrease in cardiac index and left ventricular stroke-work index, and lower MAP in comparison with balanced solutes.[32] This was also shown in our study: with increasing infusion volume, the need for vasopressors increased significantly, as did hyperchloraemic metabolic acidosis.

Another possible explanation for our results is the occurrence of profound metabolic acidosis followed by rising chloride concentrations. The latter has been shown to be severely detrimental for organ function,[32–36] especially in critically ill patients.[8,23,24,37] Metabolic acidosis has been repeatedly linked to vasodilatation[34–36] and diminished cellular function in both excitable and non-excitable tissue.[33] Profound metabolic acidosis after infusion of chloride-rich infusate in rats has been shown to increase inducible nitric oxide synthase, and thus, to lead to systemic vasodilatation and shock.[33] It has also been shown that metabolic acidosis has a profound impact on

cardiac neurotransmitter function and reactivity.[38,39] Furthermore, endogenous catecholamine synthesis is decreased during acidosis.[40]

In our study, the duration of anaesthesia was significantly longer in the normal-saline group. However, our primary outcome was not associated with the duration of anaesthesia—as shown in the logistic-regression analysis. The origin and significance of this finding remain elusive. However, it may be speculated that normal saline influences the duration of surgery. When compared with balanced infusates or colloids, it was found that the use of normal saline results in microvascular endothelial dysfunction.[41] Thus, normal saline may cause increased tissue swelling and a more complex surgical status. However, at the moment, this remains a speculation; further confirmation of this effect and, if needed, clarification of the underlying mechanisms are certainly needed before drawing any further conclusions.

Despite the growing evidence against its use, normal saline is still a widely used infusion solution in the perioperative setting and in intensive care setting.[8–13] Moreover, a Cochrane Review from 2012 came to the conclusion that, although balanced crystalloids are associated with less frequent occurrence of hyperchloraemia and concurrent metabolic acidosis, and were favoured by the authors of the review, the use of conventional solutions (i.e. saline 0.9%) can be considered safe in the perioperative period.[42] The exact mechanism underlying the observed haemodynamic instability and consequent need for vasopressor support in the present and previous studies remains unclear. However, it is plausible that hyperchloraemia alone (or in combination with metabolic acidosis)—as induced by infusion of chloride-rich solutions—is the direct trigger for unfavourable haemodynamic effects. This hypothesis should be tested in future experimental studies.[43,44]

Our study is limited by several factors: firstly, the study had to be terminated early for safety reasons. Secondly, it was only a single-centre study. Even though *post hoc* power analysis showed 90% power for norepinephrine dose per body weight (adjusted for the duration of anaesthesia), the *post hoc* power for our primary outcome was only 67%. Thirdly, the goal-directed therapy approach resulted in large volumes of fluid resuscitation, with a mean volume exceeding 3 litres.

In summary, in patients undergoing major abdominal surgery, the use of normal saline results in saline-induced hyperchloraemia with associated metabolic acidosis, and is associated with a dose-dependent increase in vasopressor requirements. Additionally, the results show that, even in patients with normal prior kidney function, the chloride load resulting from infusion of normal saline overcomes normal regulatory mechanisms in a time-/dose-dependent matter.

Authors' contributions

Study planning: C.A.P., G.L.
Study conduct: C.A.P., C.R., O.Z., B.K., E.F.
Data evaluation: C.A.P., G.C.F., G.L.
Statistical analysis: G.C.F.
Drafting manuscript: C.A.P., B.K., E.F., G.L.

Declarations of interest

None declared.

References

1. Pfortmueller CA, Fleischmann E. Acetate-buffered crystalloid fluids: current knowledge, a systematic review. *J Crit Care* 2016; **35**: 96–104
2. Verheij J, van Lingen A, Raijmakers PG, et al. Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and major vascular surgery. *Br J Anaesth* 2006; **96**: 21–30
3. Jacob M, Fellahi JL, Chappell D, Kurz A. The impact of hydroxyethyl starches in cardiac surgery: a meta-analysis. *Crit Care* 2014; **18**: 656
4. Magder S, Potter BJ, Varennes BD, Doucette S, Fergusson D. Fluids after cardiac surgery: a pilot study of the use of colloids versus crystalloids. *Crit Care Med* 2010; **38**: 2117–24
5. Sponholz C, Schelenz C, Reinhart K, Schirmer U, Stehr SN. Catecholamine and volume therapy for cardiac surgery in Germany—results from a postal survey. *PLoS One* 2014; **9**, e103996
6. Bayer O, Schwarzkopf D, Doenst T, et al. Perioperative fluid therapy with tetrastarch and gelatin in cardiac surgery—a prospective sequential analysis*. *Crit Care Med* 2013; **41**: 2532–42
7. Hans GA, Ledoux D, Roediger L, Hubert MB, Koch JN, Senard M. The effect of intraoperative 6% balanced hydroxyethyl starch (130/0.4) during cardiac surgery on transfusion requirements. *J Cardiothorac Vasc Anesth* 2015; **29**: 328–32
8. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Crit Care Med* 2014; **42**: 1585–91
9. Krajewski ML, Raghunathan K, Paluszkiewicz SM, Schermer CR, Shaw AD. Meta-analysis of high- versus low-chloride content in perioperative and critical care fluid resuscitation. *Br J Surg* 2015; **102**: 24–36
10. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely ill patients. *N Engl J Med* 2015; **373**: 1350–60
11. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Ann Surg* 2012; **255**: 821–9
12. Lobo DN. Intravenous 0.9% saline and general surgical patients: a problem, not a solution. *Ann Surg* 2012; **255**: 830–2
13. Asfar P, Schortgen F, Boisrame-Helms J, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 2017; **5**: 180–90
14. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008; **109**: 723–40
15. Wakim KG. "Normal" 0.9 per cent salt solution is neither "normal" nor physiological. *JAMA* 1970; **214**: 1710
16. Gattinoni L, Carlesso E. Supporting hemodynamics: what should we target? What treatments should we use? *Crit Care* 2013; **17**: S4
17. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg* 2012; **256**: 18–24

18. Stewart PA. Independent and dependent variables of acid-base control. *Respir Physiol* 1978; **33**: 9–26
19. Potura E, Lindner G, Biesenbach P, et al. An acetate-buffered balanced crystalloid versus 0.9% saline in patients with end-stage renal disease undergoing cadaveric renal transplantation: a prospective randomized controlled trial. *Anesth Analg* 2015; **120**: 123–9
20. WHO. *A global brief on hypertension*. 2013. Available from: http://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf?ua=1. [Accessed 5 April 2017]
21. Feldheiser A, Conroy P, Bonomo T, Cox B, Garces TR, Spies C. Development and feasibility study of an algorithm for intraoperative goal directed haemodynamic management in noncardiac surgery. *J Int Med Res* 2012; **40**: 1227–41
22. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statist* 1979; **6**: 65–70
23. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566–72
24. Nadeem A, Salahuddin N, El Hazmi A, et al. Chloride-liberal fluids are associated with acute kidney injury after liver transplantation. *Crit Care* 2014; **18**: 625
25. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest* 2004; **125**: 243–8
26. Story DA, Lees L, Weinberg L, et al. Cognitive changes after saline or plasmalyte infusion in healthy volunteers: a multiple blinded, randomized, cross-over trial. *Anesthesiology* 2013; **119**: 569–75
27. Hahn RG, Nyberg Isacson M, Fagerstrom T, Rosvall J, Nyman CR. Isotonic saline in elderly men: an open-labelled controlled infusion study of electrolyte balance, urine flow and kidney function. *Anaesthesia* 2016; **71**: 155–62
28. Berend K, van Hulsteijn LH, Gans RO. Chloride: the queen of electrolytes? *Eur J Intern Med* 2012; **23**: 203–11
29. O'Malley CM, Frumento RJ, Hardy MA, et al. A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation. *Anesth Analg* 2005; **100**: 1518–24. table of contents
30. Wilcox CS. Regulation of renal blood flow by plasma chloride. *J Clin Invest* 1983; **71**: 726–35
31. Wilcox CS, Peart WS. Release of renin and angiotensin II into plasma and lymph during hyperchloremia. *Am J Physiol* 1987; **253**: F734–41
32. Orbegozo D, Su F, Santacruz C, et al. Effects of different crystalloid solutions on hemodynamics, peripheral perfusion, and the microcirculation in experimental abdominal sepsis. *Anesthesiology* 2016; **125**: 744–54
33. Pedoto A, Caruso JE, Nandi J, et al. Acidosis stimulates nitric oxide production and lung damage in rats. *Am J Respir Crit Care Med* 1999; **159**: 397–402
34. Wray S. Smooth muscle intracellular pH: measurement, regulation, and function. *Am J Physiol* 1988; **254**: C213–25
35. Daugherty Jr RM, Scott JB, Dabney JM, Haddy FJ. Local effects of O_2 and CO_2 on limb, renal, and coronary vascular resistances. *Am J Physiol* 1967; **213**: 1102–10
36. Haddy FJ, Scott JB. Metabolically linked vasoactive chemicals in local regulation of blood flow. *Physiol Rev* 1968; **48**: 688–707
37. Di Lullo L, Bellasi A, Russo D, Cozzolino M, Ronco C. Cardiorenal acute kidney injury: epidemiology, presentation, causes, pathophysiology and treatment. *Int J Cardiol* 2017; **227**: 143–50
38. Haunstetter A, Schulze Icking B, Backs J, Kruger C, Haass M. Differential effects of acidosis, high potassium concentrations, and metabolic inhibition on noradrenaline release and its presynaptic muscarinic regulation. *Pharmacol Res* 2002; **45**: 221–8
39. Seyfarth M, Feng Y, Hagl S, Sebening F, Richardt G, Schomig A. Effect of myocardial ischemia on stimulation-evoked noradrenaline release: modulated neurotransmission in rat, guinea pig, and human cardiac tissue. *Circ Res* 1993; **73**: 496–502
40. Le Tulzo Y, Shenkar R, Kaneko D, et al. Hemorrhage increases cytokine expression in lung mononuclear cells in mice: involvement of catecholamines in nuclear factor-kappaB regulation and cytokine expression. *J Clin Invest* 1997; **99**: 1516–24
41. Torres LN, Chung KK, Salgado CL, Dubick MA, Torres Filho IP. Low-volume resuscitation with normal saline is associated with microvascular endothelial dysfunction after hemorrhage in rats, compared to colloids and balanced crystalloids. *Crit Care* 2017; **21**: 160
42. Burdett E, Dushianthan A, Bennett-Guerrero E, et al. Perioperative buffered versus non-buffered fluid administration for surgery in adults. *Cochrane Database Syst Rev* 2012; **12**, CD004089
43. Boer C, Bossers SM, Koning NJ. Choice of fluid type: physiological concepts and perioperative indications. *Br J Anaesth* 2018; **120**: 384–96
44. McLean DJ, Shaw AD. Intravenous fluids: effects on renal outcomes. *Br J Anaesth* 2018; **120**: 397–402

Handling editor: C. Boer