Does a balanced colloid decrease perioperative blood loss in paediatric cardiac surgery: a double-blinded randomized controlled trial?

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ORIGINAL ARTICLE

Does a balanced colloid decrease perioperative blood loss in paediatric cardiac surgery

A double-blinded randomized controlled trial?

Ariane Willems, Françoise De Groote, Denis Schmartz, Jean-François Fils and Philippe Van der Linden

BACKGROUND Unbalanced fluid solutions cause metabolic acidosis and could be associated with impaired coagulation and increased blood loss.

OBJECTIVE To investigate whether the use of a balanced colloid compared with a saline colloid for peri-operative fluid therapy in children undergoing cardiac surgery is associated with decreased blood loss and exposure to blood products.

DESIGN Double-blinded randomised controlled trial.

SETTING Tertiary children's hospital from 2013 to 2016.

PATIENTS Children older than 29 days and younger than 3 years admitted for cardiac surgery with cardiopulmonary bypass (CPB). Exclusion criteria were emergency cardiac surgery, moribund (American Society of Anesthesiologists 5), Jehovah's witnesses, coagulopathy, renal failure, liver injury, intracranial haemorrhage and electrolyte disturbances. From the 128 patients eligible, 88 were included in the study.

INTERVENTION Random assignment of patients to either a saline colloid (6% hydroxyethyl starch 130/0.4 in 0.9% NaCl) or a balanced-electrolyte colloid (6% hydroxyethyl starch 130/0.4 in an isotonic solution) for CPB priming and intra- and postoperative fluid therapy during the first postoperative 48 h.

MAIN OUTCOME MEASURE The primary outcome measure was calculated blood loss until the third postoperative day (POD3).

RESULTS A total of 44 patients were included in each study arm. Calculated blood loss at POD3 was not significantly different between the groups (saline colloid 19.9 [IQR 13.8 to 26.1] ml kg^{-1} versus balanced colloid 15.9 [IQR 9.0 to 25.3 ml kg^{-1}], $P = 0.409$). Secondary outcomes related to bleeding, exposure to blood products and coagulation were not different between groups. There was also no difference in length of mechanical ventilation, intensive care and hospital length of stay between groups.

CONCLUSION The use of a balanced colloid for peri-operative fluid therapy compared with a saline one is not associated with decreased blood loss or exposure to blood products.

TRIAL REGISTRATION EudraCT identifier: 2012-006034-17 and ClinicalTrial.gov identifier: NCT02584868.

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Introduction

Colloids are frequently used for fluid replacement therapy to ensure haemodynamic stability and to compensate for blood loss in major surgery when fluid replacement with crystalloids alone is not considered sufficient. In cardiac surgery, colloids are also used for cardiopulmonary bypass (CPB) priming where large amounts of fluids are necessary, in order to reduce peri-operative fluid balance.[1] In children, the amount of fluid needed for CPB priming can exceed their own circulating blood volume depending on their age and weight. Tetrastarches, the latest generation of hydroxyethyl starches, are used in some centres as they have a comparable efficacy and safety profile as human albumin 4%.[2–7]

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Colloids diluted in saline (NaCl 0.9%) are associated with hyperchloraemic metabolic acidosis due to the large amount of chloride present in the solution. Clinical consequences of a hyperchloraemic metabolic acidosis are still debated in the literature. Beside its well-known adverse effect on the cardiovascular system, metabolic acidosis could be associated with impaired haemostasis through its deleterious effect on coagulation enzymes and platelet function, resulting in increased peri-operative blood loss.[8,9] Cardiac surgery is considered a high bleeding risk procedure, particularly in children, and bleeding has been associated with increased morbidity and mortality in this vulnerable population.[10,11]

In recent years, colloids with a balanced electrolyte solution containing less chloride have been developed. The use of a balanced-electrolyte colloid might reduce metabolic acidosis and its deleterious effects on coagulation. We tested this hypothesis in a randomised controlled trial (RCT) comparing a balanced-electrolyte tetrastarch with a saline-based tetrastarch solution in children undergoing cardiac surgery on calculated blood loss until postoperative day 3 (POD3).

Methods

This double-blinded RCT was conducted in a tertiary children's hospital and started in 2013. We assigned patients randomly to receive either 6% hydroxyethyl starch 130/0.4 in an isotonic solution of electrolytes (Volulyte, Fresenius Kabi GMbH, Bad Homburg, Germany) or 6% hydroxyethyl starch 130/0.4 in 0.9% NaCl (Voluven, Fresenius Kabi GMbH) for CPB priming and intra- and postoperative fluid therapy during the first postoperative 48 h with a maximum dose of 50 ml kg^{-1} day^{-1} as recommended at that time. No interim safety analysis was planned. Suspected unexpected serious adverse events and serious adverse events were recorded during the study and declared as appropriate.

In June 2013, the European Medicines Agency (EMA) initiated a process of agreeing to reduced indications for the use of hydroxyethyl starches. In 2016, the EMA Pharmacovigilance Risk Assessment Committee recommended the suspension of the marketing authorisations for hydroxyethyl starch (HES) solutions for infusion and plasma volume replacement across the European Union (https://www.ema.europa.eu/en/news/prac-recommends-suspending-hydroxyethyl-starch-solutions-infusion-market). The study was therefore suspended in 2016 waiting for a definitive EMA conclusion. In 2018, the Coordination Group for Mutual Recognition and Decentralised Procedures – Human of the EMA decided that HES solutions for infusion should remain on the market provided that a combination of additional measures to protect patients was implemented. One of these measures is the restriction of the maximal dose to less than 30 ml kg^{-1} and for a duration less than 24 h (https://www.ema.europa.eu/en/news/hydroxyethyl-starch-solutions-cmdh-introduces-new-measures-protect-patients). As those measures are incompatible with the protocol of the trial, the study had to be terminated.

Ethical approval for this study (CEH n° 32/12) was provided by the Institutional Review Board of the Queen Fabiola University Children's Hospital, Brussels, Belgium (Chairperson: Dr J. Grosswasser) (CEH n° 32/12) on 27 April 2012. Written informed consent was sought from parents or surrogate decision-makers of all patients participating in the trial. This clinical trial was authorised by the Belgian Federal Agency for Medicine and Health Products on 27 March 2012 (EudraCT: 2012-006034-17). The trial was registered prior to patient enrolment on 14 March 2012 (NCT02584868; Principal investigator: Philippe Van der Linden). This manuscript adheres to the applicable CONSORT guidelines for randomised controlled trials.[12]

All consecutive children admitted for cardiac surgery with CPB at the University Children's Hospital Queen Fabiola in Brussels were screened. Children aged between 30 days and 3 years were enrolled. Exclusion criteria were neonates (<30 days of life), emergency cardiac surgery, moribund (defined as an American Society of Anesthesiologists physical status of 5), Jehovah's witnesses, presence of a coagulopathy at screening defined as platelet count $< 100 \times 10^9$ l^{-1} and/or a prothrombin time <70% and/or an activated partial thromboplastin time (aPTT) >35 s and/or fibrinogen <1 g l^{-1}, presence of renal failure preoperatively defined as a creatinine >132 μg l^{-1} and/or patient receiving renal replacement therapy, presence of liver injury defined as aspartate aminotransferase and/or alanine aminotransferase >80 IU l^{-1}, presence of an intracranial haemorrhage, and pre-operative electrolyte disturbances with Na >150 mmol l^{-1} and/or Cl >110 mmol l^{-1}.

Randomisation was performed by the pharmacist of the hospital using an internet-based software programme (http://www.randomization.com). Patients were assigned to the study groups in blocks of 10 and were randomly distributed and stratified according to the presence or not of cyanotic heart disease and three weight groups (<5 kg, 5 to 12 kg, and >12 kg) at randomisation. The study was double-blinded. On the morning of surgery, the pharmacist prepared the blinded solutions by apposition of a sticker on both sides of the hydroxyethyl starch solution bag preventing visibility of the name and composition of the solution. Physicians, nurses and research staff were unaware of the block randomisation strategy.

Patients received either 6% hydroxyethyl starch 130/0.4 in a balanced isotonic solution of electrolytes (Volulyte) or 6% hydroxyethyl starch 130/0.4 in 0.9% NaCl (Voluven) for CPB priming and intra- and postoperative fluid therapy during the first postoperative 48 h with a maximum dose of 50 ml kg^{-1} day^{-1}. For intra-operative volume replacement before or after CPB, the amount of

colloid not used for priming could be given, up to the maximum dosage for the individual patient, if needed. No specific algorithm for fluid administration was used. Infusion rates were adjusted to individual needs at the discretion of the anaesthesiologist in charge of the patient. If the maximum dose of study colloid was reached, human albumin 4% was used as a rescue colloid. No crystalloids were administered intra-operatively for fluid resuscitation. In the paediatric intensive care unit (PICU), maintenance fluid was restricted to one third of total fluid needs. Six hours after admission, enteral feeding was started and no maintenance crystalloids were administered. If needed, 4% plasma protein solution (SOPP-SSPP 4%, Sanquin, Amsterdam, The Netherlands), a colloid based on human albumin, was used for volume replacement. Except for priming of the CPB circuit (Supplemental File 1, http://links.lww.com/EJA/A553), no sodium bicarbonate was administered during surgery or in the postoperative period to correct acid-base balance. The composition of both colloids used is presented in Supplemental File 2, http://links.lww.com/EJA/A554.

Anaesthetic and postoperative intensive care management were standardised during the whole study period as has already been described.[7] A detailed overview can be found in the Supplemental file 1, http://links.lww.com/EJA/A553. All patients were anaesthetised by the same small group of anaesthesiologists and all operations were performed by the same surgeon.

Preoperative characteristics, severity scores and intra-operative data were noted. Cardiac surgical procedures were categorised according to the Risk Adjusted Classification for Congenital Heart Surgery-1.[13] Intra-operative data included surgery, CPB and aortic cross clamp duration. The use of an aortic cross clamp (yes/no) and circulatory arrest (yes/no) was also noted.

Blood gases were analysed at different time points with a SIEMENS RapidPoint 500 (Siemens Healthcare GmbH, Erlangen Germany) which determined the actual HCO_3 value (HCO_3-act) directly from pH and PCO_2 values as recommended by the National Committee for Clinical Laboratory Standards. The different time points were: intra-operatively before CPB (T0) and after discontinuation of CPB (T1); postoperatively at admission (H0) and 8 h after admission to the PICU (H8) and at postoperative days (POD) 1 and 2.

Inotropic support defined by the vasoactive inotrope score[14] after separation from CPB and the highest value during the first 48 h postoperatively were calculated.

The primary outcome, 'calculated blood loss at POD3' was quantified using a formula taking into account preoperative and postoperative haematocrit at POD3, estimated blood volume and amount of packed red blood cells (RBCs) for CPB priming and during and after surgery until POD3, as described in Hanart *et al.*[2] Calculated blood loss was preferred over measured blood loss because intra-operative measured blood losses are imprecise and postoperative chest tube drainage does not take into account the haematocrit of the volume lost and therefore overestimates the real RBC mass loss.[15,16]

Metabolic acidosis was defined as a pH <7.35. Hyperchloraemia was defined as a serum chloride concentration >110 mmol l^{-1}. This cut-off was chosen based on our laboratory's upper limit of normal and the literature. Severe hyperchloraemia was defined as a serum concentration >115 mmol l^{-1}.[17,18] Cut-off value for HCO_3 was 23 mmol l^{-1} and for base excess,-5. For pH, chloride, HCO_3 and base excess worst values during the study period were compared between groups.

Secondary outcomes were exposure to blood products defined as any administration of packed RBCs, fresh frozen plasma (FFP) or platelets during surgery or postoperatively until POD3 and measured blood loss determined intra-operatively by weighing surgical sponges and measuring blood loss in volumetric containers after surgical aspiration, and postoperatively in chest tubes. Coagulation profiles were compared using the standard coagulation tests prothrombin time, aPTT and fibrinogen at different time points and thromboelastometry using rotational thromboelastometry (ROTEM) (EXTEM assay using Tissue Factor to monitor the Extrinsic Pathway) and FIBTEM (FIBTEM assay that monitors clot firmness after blocking the contribution of platelets by adding Cytochalasin D). ROTEM was performed as part of the study protocol at two time points: before surgical incision and 10 min after protamine administration.

Other studied clinical outcomes were duration of mechanical ventilation, postoperative extracorporeal membrane oxygenation (ECMO), intensive care (ICU) and hospital lengths of stay and in-hospital death.

Statistical analysis

The sample size estimation was based on the subgroup of children between 1 month and 3 years included in a previous study where calculated blood loss at POD3 was 26.5 ± 13.07 ml kg^{-1} in the hydroxyethyl tetrastarch group (Voluven).[2] In order to detect an absolute reduction of 25% (6.5 ml kg^{-1}) in the balanced hydroxyethyl tetrastarch group (Volulyte), with a two-sided alpha of 5% and a power of 80%, we would need to enrol 70 patients in each group (140 patients in total) in order to recruit 63 patients in each group after allowance for withdrawals.[2]

All analyses were based on the intention-to-treat principle. Continuous variables are presented as median [IQR] or mean ± SD, and compared using the Wilcoxon Rank Sum or *t*-test, as appropriate (residuals of the *t*-test were tested for normality using a Kolmogorov-Smirnov normality test). Categorical variables are presented as

frequencies and percentages and compared with the χ^2 test. Results were considered significant if $P < 0.05$.

A mixed between-within subjects' analysis of variance was conducted to assess the impact of the two different tetrastarches on pH, chloride, bicarbonate and base excess across different time periods (preoperative, after discontinuation of CPB, at admission to the PICU, 8 h after admission to the PICU and at POD1 and POD2). Interaction was tested with the Wilks-Lambda test. The main effect comparing both fluids was considered significant if $P < 0.05$. Adjustments of P values were made for multiple comparisons (Bonferroni); a P value < 0.0007 was considered statistically significant. Data were analysed with SPSS, version 25 (IBM SPSS software).

Post hoc, a conditional power analysis for a hypothetical interim analysis at two thirds of the final sample size, was performed with these data to estimate the probability of a significant result if the study was completed. The default parameters of the rpact R package (R software version 3.6) were used for this group-sequential analysis.

Results

From 14 February 2013 to 11 November 2016, a total of 127 patients were eligible for inclusion. Of these, 12 (9%) met at least one exclusion criterion. For 22 (17%) of the remaining patients, parents declined to give consent. We therefore randomly assigned 93 children to the two study groups. Of those, five children were withdrawn after randomisation [surgery without CPB ($n = 4$); no surgery ($n = 1$)], leaving 88 patients for analysis (44 in each group) (Fig. 1). Before being discontinued, the study was temporarily suspended between 2016 and 2018, losing 66 patients for potential inclusion.

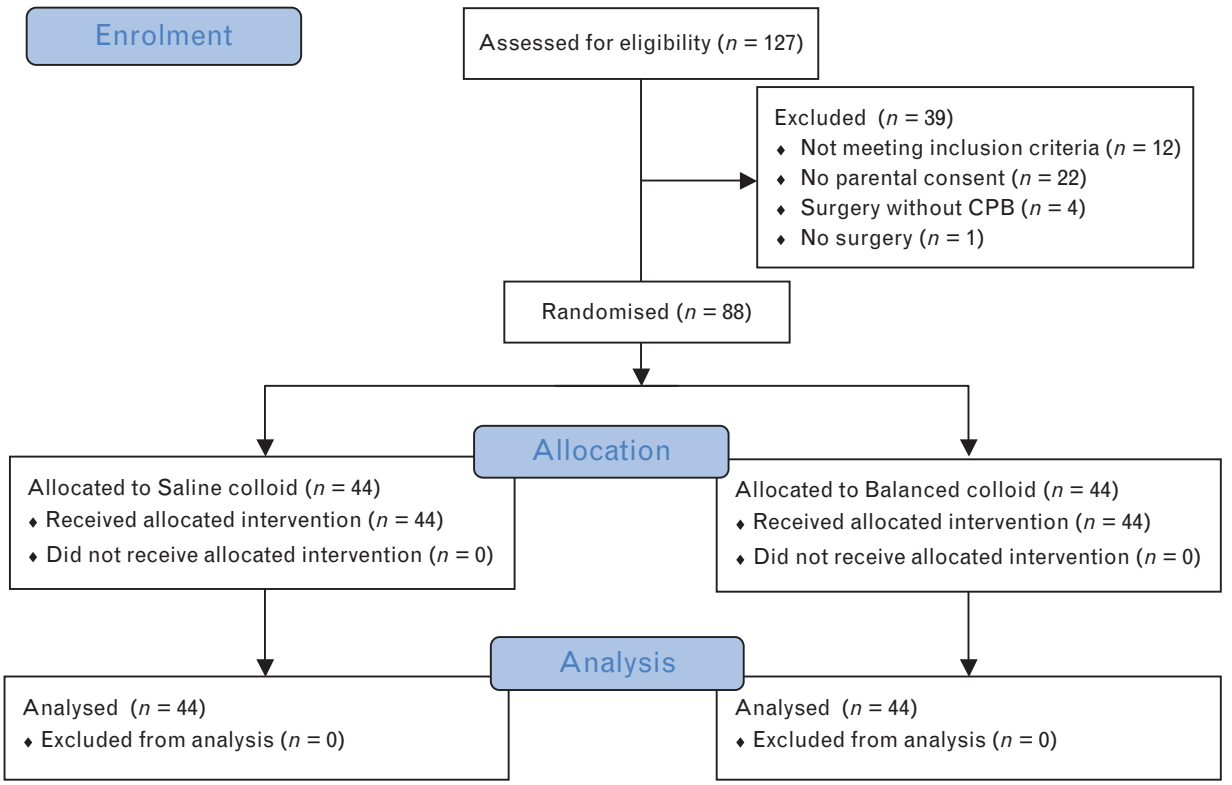
Patients in the two study groups had similar preoperative characteristics, severity scores and intra-operative data at baseline (Table 1).

Similar volumes of the study colloid were administered intra- and postoperatively. The numbers of patients receiving the study colloid and the rescue colloid human albumin postoperatively were also similar. There were no significant differences between groups for either intra-operative or first postoperative 48 h fluid balance. All administered crystalloids peri-operatively and postoperatively were similar between groups. Finally, no difference in inotropic support was observed between groups (Table 2).

Primary outcome

The primary outcome measure, calculated blood loss at POD3, was not statistically significantly different between the groups (saline colloid 19.9 [IQR 13.8 to

Fig. 1 Study flow chart



CPB, cardiopulmonary bypass.

Table 1 Pre-operative characteristics, severity scores and intra-operative data

Variables	Saline colloid	Balanced colloid
Number of patients	44	44
<5 kg	12	10
5 to 12 kg	30	33
12 to 20 kg	2	1
Elective surgery	44 (100)	44 (100)
Sex, male	20 (45.5)	26 (59.1)
Age, months	6.3 [4.5 to 13.7]	6.9 [5.2 to 16.1]
Preoperative weight, kg	6.5 [5.0 to 8.9]	6.9 [5.0 to 9.0]
Cyanotic heart disease, yes	23 (52.3)	23 (52.3)
Preoperative S_pO_2, %	93 [80 to 98]	94 [81 to 98]
Univentricular heart, yes	5 (11.4)	7 (15.9)
ASA physical status		
2	2 (4.5)	4 (9.1)
3	39 (88.6)	36 (81.8)
4	3 (6.8)	4 (9.1)
Redo surgery	3 (6.8)	3 (6.8)
RACHS-1 score		
Risk category 1	3 (6.8)	2 (4.5)
Risk category 2	21 (47.7)	26 (59.1)
Risk category 3	11 (25.0)	8 (18.2)
Risk category 4	8 (18.2)	8 (18.2)
Risk category 6	1 (2.3)	0 (0.0)
CPB priming volume, ml kg^{-1}	41.6 [34.1 to 52.1]	42.5 [34.2 to 48.2]
CPB haemodilution, %	52.0 [42.6 to 65.2]	53.1 [44.7 to 60.3]
Surgery time, min	224.5 ± 64.9	219.7 ± 57.5
CPB time, min	114.2 ± 44.2	116.9 ± 43.0
Aortic cross clamp time, min	56.3 ± 27.2	56.4 ± 27.1
Aortic cross clamp, yes	42 (95.5)	41 (93.2)
Circulatory arrest, yes	3 (6.8)	2 (4.5)
Minimum temperature, °C	32.0 [31.3 to 32.0]	32.0 [30.3 to 32.0]
MUF	42 (100.0)	42 (97.7)
MUF volume, ml kg^{-1}	35.8 [27.2 to 42.9]	33.9 [25.3 to 46.2]

Values are median [IQR], mean ± SD or number (%). ASA, American Society of Anesthesiologists; CPB, cardiopulmonary bypass; MUF, modified ultrafiltration; RACHS-1, Risk Adjusted Classification for Congenital Heart Disease; S_pO_2, oxygen saturation by pulse oximetry.

26.1] ml kg^{-1} versus balanced colloid 15.9 [9.0 to 25.3] ml kg^{-1}, $P = 0.409$) (Table 3). The conditional power analysis indicates that a difference between the two groups could be found with a probability of 2.15%.

Table 3 Chloride and acid-base status in each group

Variables	Saline colloid	Balanced colloid	P
Number of patients	44	44	
pH			
pH at end of CPB (T1)	7.31 ± 0.06	7.35 ± 0.05	0.001
Patients with pH <7.35	40 (90.9)	34 (77.3)	0.143
Lowest pH during study period	7.27 ± 0.06	7.31 ± 0.04	<0.001
Chloride anion, mmol l^1 (Cl^-)			
Cl^- at end of CPB (T1)	112.3 ± 3.5	110.2 ± 2.6	0.001
Patients with Cl^->110 mmol l^{-1}	33 (75.0)	22 (50.0)	0.027
Patients with severe hyperchloraemia (Cl^->115 mmol l^{-1})	10 (22.7)	2 (4.5)	0.026
Highest Cl^- during study period	111.5 ± 3.4	109.4 ± 2.6	0.001
Bicarbonate, mmol l^{-1} (HCO_3^-)			
HCO_3^- at end of CPB (T1)	22.7 ± 3.7	23.3 ± 3.0	0.393
Patients with lowest HCO_3^- <23 mmol l^{-1}	38 (88.4)	35 (81.4)	0.549
Lowest HCO_3^- during study period	18.5 ± 4.4	20.5 ± 2.3	0.009
Base excess, mmol l^{-1} (BE)			
BE at end of CPB (T1)	−6.1 ± 3.2	−3.4 ± 2.4	<0.001
Patients with BE <−5 during study period	34 (77.3)	18 (40.9)	0.001
Lowest BE during study period	−6.9 ± 3.2	−5.2 ± 4.6	0.052

Values are mean ± SD or number (%).BE, base excess; CPB, cardiopulmonary bypass.

Secondary analyses

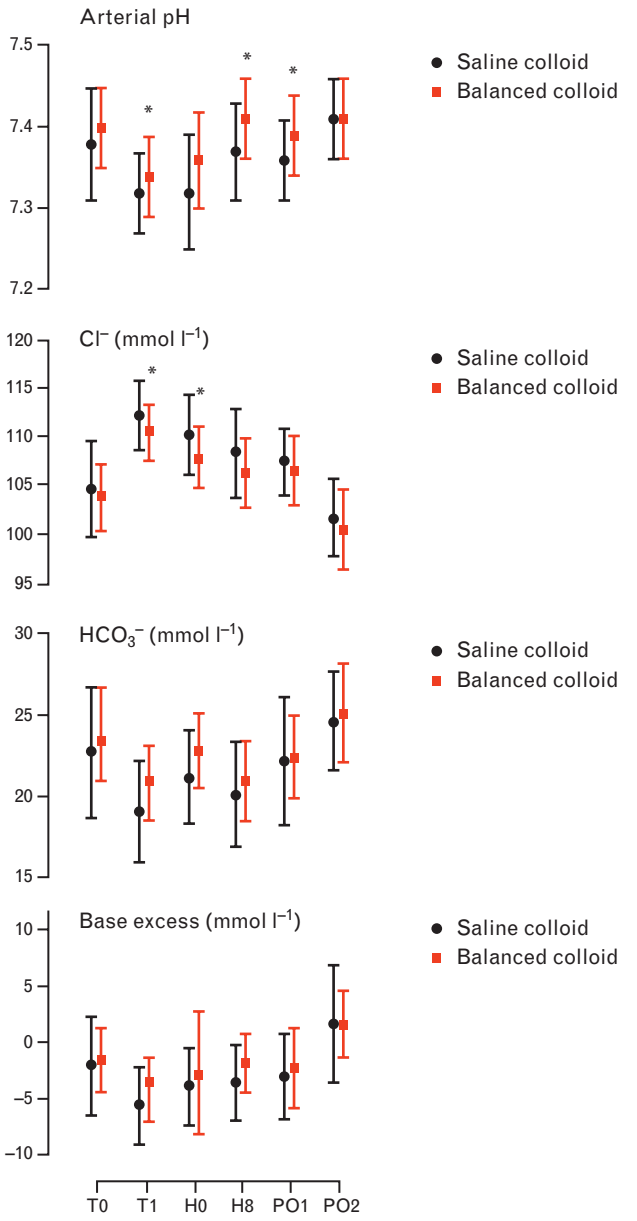
The values of pH, chloride, base excess and HCO_3 over time were compared and are shown in Figure 2. Chloride concentration was higher and metabolic acidosis more profound in the saline colloid group and normalised by POD 2. Arterial pH was significantly lower at time points T1, H8 and POD1 and chloride was significantly higher at time points T1 and H0, in the saline colloid group. The pH, chloride and BE were statistically different after the end of CPB (T1) between groups. Significantly more patients presented with hyperchloraemia and a base excess less than -5 in the saline colloid group during the study period. Finally, extreme values of pH, chloride,

Table 2 Intervention, administration of other colloids, fluid balance and inotropic support intra-operatively and first 48 h postoperatively

Variables	Saline colloid	Balanced colloid	P
Number of patients	44	44	
Study colloid			
Intra-operative (total), ml kg^{-1}	34.5 [27.5 to 44.8]	33.9 [28.3 to 42.4]	0.674
Patients receiving HES postoperatively	30 (68.2)	26 (59.1)	0.375
Postoperative (first 48 h), ml kg^{-1} in patients receiving HES	10.3 [7.4 to 16.5]	12.9 [5.9 to 16.4]	0.599
4% HA solution			
Patients receiving 4% HA solution postoperatively	22 (50.0)	22 (50.0	1.000
Postoperative (first 48 h), ml kg^{-1} in patients receiving 4% HA solution	12.1 [9.7 to 20.0]	18.4 [10.0 to 24.6]	0.193
Crystalloids			
Intra-operative (total), ml kg^{-1}	32.7 [28.1 to 37.5]	34.8 [27.1 to 47.2]	0.614
Cardioplegia, ml kg^{-1}	24.2 [20.0 to 27.7]	24.1 [20.0 to 29.8]	0.525
POD 0, ml kg^{-1}	38.9 [27.2 to 47.2]	33.1 [6.9 to 46.7]	0.353
Fluid balance			
Intra-operative, ml kg^{-1}	16.1 ± 21.4	17.5 ± 25.6	0.979
Postoperative (first 48 h), ml kg^{-1}	29.5 ± 27.6	30.3 ± 27.6	0.905
Inotropic support			
Peri-operative VIS (after discontinuation of CPB)	5.0 [3.3 to 10.8]	5.0 [3.0 to 15.0]	0.867
Worst VIS postoperatively	9.0 [5.0 to 17.5]	6.0 [5.0 to 26.0]	0.866

Values are median [IQR], mean ± SD or number (%). CPB, cardiopulmonary bypass; HA, Human albumin; HES, hydroxyethyl starch; VIS, vasoactive inotrope score.

Fig. 2 Postoperative evolution over time of pH, base excess and HCO_3 in both groups



Comparison of serum chloride concentration (interaction Wilks-Lambda $P = 0.212$; test of between-subjects effects $P = 0.003$); pH (interaction Wilks-Lambda $P = 0.142$; test of between-subjects effects $P = 0.010$); HCO_3 (interaction Wilks-Lambda $P = 0.246$; test of between-subjects effects. $P = 0.118$) and base excess (interaction Wilks-Lambda $P = 0.026$; test of between-subjects effects $P = 0.119$). The different time points were: intra-operatively before CPB (T0) and after separation of CPB (T1); postoperatively at admission (H0) and 8 h after admission to the PICU (H8) and at postoperative days (POD) 1 and 2. $P < 0.007$ was considered a significant difference between groups at each time point and these are marked with an asterisk.

HCO_3 and base excess were significantly different between groups (Table 3). Secondary outcomes relating to exposure to blood products and bleeding are shown in Table 4. The number of patients exposed to any blood product was not different between the groups. Regarding the different blood products separately, there was no difference between groups in the number of patients transfused or in the volume administered. Measured intra- and postoperative blood loss was not significantly different between groups.

Results of coagulations tests are shown in Supplemental Appendix 1, http://links.lww.com/EJA/A552. Intra- and postoperative standard coagulation tests at different time points and intra-operative EXTEM and FIBTEM ROTEM data were not statistically different between groups.

Other clinical outcomes were not different between groups. There were no differences between groups in median [IQR] ventilator-free days (saline colloid 27 [26 to 27] versus balanced colloid 27 [25 to 28] days, $P = 0.734$); duration of mechanical ventilation (saline colloid 26 [13 to 53] versus balanced colloid 21 [9 to 72] h, $P = 0.670$); ICU-free days (saline colloid 24 [20 to 25] versus balanced colloid 23 [21 to 25] days, $P = 0.987$); ICU stay (saline colloid 5 [3 to 8] versus balanced colloid 5 [3 to 6] days, $P = 0.997$) and hospital length of stay (saline colloid 12 [8 to 17] versus balanced colloid 11 [8 to 14] days, $P = 0.786$). There were also no differences in the number (%) of patients who required ECMO [saline colloid 0 (0%) versus balanced colloid 0 (0%), $P = 1.000$] or died during hospital stay [saline colloid 1 (2.3%) versus balanced colloid 0 (0%), $P = 0.315$].

Discussion

When compared with a saline colloid, the use of a balanced electrolyte colloid for CPB priming and perioperative fluid therapy led to more stable acid-base conditions and chloride concentrations but was not associated with a significant reduction in calculated blood loss by POD3 in children undergoing cardiac surgery. Accordingly, exposure to allogeneic blood products was not different between the two groups. These results indicate that, even used at a maximal dose (as recommended at the time) of 50 ml kg^{-1}, the solvent used in the colloid solution appears to have minimal impact on peri-operative haemostasis. This observation is confirmed by the fact that postoperative conventional and viscoelastic coagulations tests were not different between the saline colloid and balanced colloid groups. Although children in the Saline colloid group exhibited a lower pH during the intra- and the immediate postoperative periods, this effect might not have been sufficiently pronounced to alter the patients' haemostasis. Indeed, some authors have reported that the pH needs to be as low as 7.1 to observe the deleterious effect of acidosis on coagulation.[19] Duration of mechanical ventilation and ventilator-free days was not different between groups, further indicating that the acidosis was moderate and not clinically relevant as it was not necessary to take action to

Table 4 Primary and secondary outcomes related to bleeding and transfusion

Variables	Saline colloid	Balanced colloid	*P*
Number of patients	44	44	
Primary outcome			
Calculated blood loss at POD3, ml kg^{-1}	19.9 [13.8 to 26.1]	15.9 [9.0 to 25.3]	0.409
Secondary outcomes			
Blood loss			
Intra-operative blood loss, ml kg^{-1}	4.7 [2.8 to 7.2]	4.8 [2.9 to 6.4]	0.881
Chest tube drainage, ml kg^{-1}			
First 24 h	14.3 [10.0 to 19.3]	14.9 [11.6 to 20.4]	0.556
Total	18.8 [11.8 to 27.7]	18.8 [14.8 to 28.3]	0.796
Total blood loss, ml kg^{-1}	25.7 [18.7 to 34.0]	23.4 [18.4 to 34.1]	0.953
Transfusions			
Exposure to any blood product	36 (81.8)	30 (68.2)	0.140
Exposure to RBC with priming	35 (79.5)	30 (68.2)	0.225
Exposure to RBC without priming	15 (34.1)	16 (36.4)	0.823
RBC transfused (with priming) in transfused patients, ml kg^{-1}	21.9 [18.4 to 38.5]	26.1 [15.7 to 44.4]	0.892
RBC transfused (without priming) in transfused patients, ml kg^{-1}	19.8 [15.2 to 24.3]	20.1 [13.9 to 28.3]	0.800
Exposure to FFP	4 (9.3)	4 (9.3)	1.000
FFP transfusion, ml kg^{-1}	12.6 [9.3 to 46.4]	12.2 [10.1 to 26.8]	0.886
Exposure to platelets	2 (4.5)	0 (0)	0.153
Platelet transfusion, ml kg^{-1}	13.7 ± 6.4	0 ± 0	–

Values are median [IQR], mean ± SD or number (%). FFP, fresh frozen plasma; POD, postoperative day; RBC, red blood cell.

compensate for it and had no impact on the duration of ventilation.

Furthermore, acidosis caused by unphysiologically composed saline-based fluids is a consequence of chloride overload and its impact on acid-base balance depends also on the infusion volume. In a randomised controlled open trial comparing a balanced and an unbalanced crystalloid in children undergoing major surgery, Disma *et al.*[20] reported that the risk of developing hyperchloraemia was significantly higher when larger volumes (over 47 ml kg^{-1}) were infused regardless of type of crystalloids used. In our study, some patients in the balanced colloid group also developed hyperchloraemia, although the incidence was significantly less than in the saline colloid group. In our study, the dose of 50 ml kg^{-1} was administered only on the day of surgery, which may explain why hyperchloraemia normalised rapidly in the immediate postoperative period. Finally, ROTEM maximum clot firmness (MCF) was low. We also know that HES impairs fibrin polymerisation and its use is associated with reduced MCF, which could be associated with increased blood loss.[21] However, its impact on peri-operative blood loss remained debated.[5] In our population, we had no reintervention for haemorrhage and low exposure to transfusions compared with the literature.[22,23] Other colloids also have drawbacks. Human albumin exists only diluted in saline, geloplasma (gelatine diluted in a balanced solution) is hypotonic and hypooncotic, and both carry a higher risk of anaphylaxis.[24] Finally, a recent study showed no benefit of CPB priming with FFP over a balanced-electrolyte colloid solution with regard to blood loss and transfusion.[25]

To our knowledge, there is no previous literature comparing the effect of the colloid solvent (balanced or saline-based) on peri-operative blood loss in paediatric cardiac surgery. In adults undergoing cardiac surgery, literature is scarce and the number of patients included in the few published studies is small. In one RCT using a similar design as ours, Base *et al.*[26] showed that the use of a balanced-electrolyte colloid was associated with a less severe metabolic acidosis without significant impact on outcome measures. However, the authors did not study the effect of their fluid strategy on coagulation tests, bleeding or transfusion. In an open-label pilot study comparing a saline-based gelatin to a balanced-electrolyte tetrastarch for CPB priming, coagulation was significantly impaired in the HES group as measured with FIBTEM MCF but was not associated with higher blood loss and transfusions.[27] In that study, both dilution solution and type of colloid were different, making it impossible to differentiate the effects of the colloid itself from those related to the solvent solution.

In both children and adults undergoing cardiac surgery, it seems that the use of balanced-electrolyte colloids is associated with less profound metabolic acidosis that does not translate into a relevant effect on clinical outcome. However, only a few studies address this topic in children. From a theoretical point of view, hyperchloraemia may complicate the interpretation of a postoperative metabolic acidosis, certainly in unstable patients. In this context, it may be interesting to administer balanced-electrolyte colloids in the peri-operative period of cardiac surgery. Further studies are needed to study the impact of balanced-electrolyte colloids on other outcomes, such as kidney injury, as hyperchloraemia is associated with renal vasoconstriction.

Strengths and limitations

To our knowledge, this is the first double-blinded RCT comparing a colloid diluted in a balanced electrolyte

solution with a colloid in saline for peri-operative fluid replacement in children undergoing cardiac surgery. Other strengths of this study are that we compared the same colloid, namely HES, making a comparison solely on the solvent fluid and decreasing the risk of interference with the presence of, or the nature of, the colloid on the different outcomes. Third, patients received large amounts of the studied fluids ($50\,ml\,kg^{-1}$; maximum recommended dose at that time) allowing us to study the real impact of the solvent solution on patients' outcomes. Fourth, patients were stratified based on their weight to address the effect of haemodilution on outcomes. Fifth, we used well defined and standardised outcome variables to increase reproducibility. Finally, as all operations were performed by the same surgeon, there was no variation in quality of surgical haemostasis that could affect outcomes.

Our study has also some limitations. The most important one was that the study was ended prematurely with inclusion of fewer patients than needed with the consequence that the study was underpowered to demonstrate a significant difference in primary outcome. Conditional power analysis was equal to 2.15% meaning that the probability of obtaining a significant result at the end of the trial would have been very low if we pursued the study, given the interim data. Second, exclusion of neonates and inclusion of patients with no more than moderate severity (mostly RACHS $\leq$3) imply that we cannot infer conclusions on the effect of a balanced-electrolyte colloid on bleeding and transfusion in those populations who are at higher risk of bleeding. Third, we cannot exclude that some unmeasured co-interventions or medications could have influenced the results. Finally, this single-centre study may weaken the generalisation and extrapolation of the results.

Conclusions

The results of the study suggest that the solvent composition of the colloid used (saline versus balanced electrolyte) probably does not impact blood loss and transfusion of blood products in children undergoing cardiac surgery. Further larger well-powered studies are warranted to define strong conclusions on possible benefits of balanced-electrolyte colloids in this population.

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