Efficacy and safety of 6% hydroxyethyl starches 130/0.4 (Voluven®) for perioperative volume replacement in children undergoing cardiac surgery: a propensity-matched analysis

Critical Care (2015) 19:87


Philippe Van der Linden (philippe.vanderlinden@chu-brugmann.be)
Melanie Dumoulin (melanie.dumoulin@ulb.ac.be)
Celine Van Lerberghe (celine.van.lerberghe@ulb.ac.be)
Cristel Sanchez Torres (cristel.sancheztorres@huderf.be)
Ariane Willems (ariane.willems@huderf.be)
David Faraoni (davidfaraoni@icloud.com)

Published online: 17 March 2015

ISSN 1364-8535
Article type Research
Submission date 15 August 2014
Acceptance date 20 February 2015
Article URL http://dx.doi.org/10.1186/s13054-015-0830-z

Like all articles in BMC journals, this peer-reviewed article can be downloaded, printed and distributed freely for any purposes (see copyright notice below).

Articles in BMC journals are listed in PubMed and archived at PubMed Central.

For information about publishing your research in BMC journals or any BioMed Central journal, go to http://www.biomedcentral.com/info/authors/

© 2015 Van der Linden et al.; licensee BioMed Central. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Efficacy and safety of 6% hydroxyethyl starches 130/0.4 (Voluven®) for perioperative volume replacement in children undergoing cardiac surgery: a propensity-matched analysis

Philippe Van der Linden1*
* Corresponding author
Email: philippe.vanderlinden@chu-brugmann.be

Melanie Dumoulin1
Email: melanie.dumoulin@ulb.ac.be

Celine Van Lerberghe1
Email: celine.van.lerberghe@ulb.ac.be

Cristel Sanchez Torres1
Email: cristel.sancheztorres@huderf.be

Ariane Willems2
Email: ariane.willems@huderf.be

David Faraoni3
Email: davidfaraoni@icloud.com

1 Department of Anesthesiology, University Hospital Brugmann and Queen Fabiola Children's University Hospital, Free University of Brussels, 4 Place Van Gehuchten, B-1020, Brussels, Belgium

2 Pediatric Intensive Care Unit, Queen Fabiola Children’s University Hospital, Free University of Brussels, Brussels, Belgium

3 Department of Anesthesiology, Peri-operative and Pain Medicine. Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA

Abstract

Introduction

Six percent hydroxyethyl starch (HES) 130/0.4 is considered as an alternative to human albumin (HA) and crystalloids for volume replacement in children undergoing cardiac surgery. In this large propensity-matched analysis, we aimed to assess efficacy and safety of replacing HA with HES for intra-operative volume therapy in children undergoing cardiac surgery with cardiopulmonary bypass (CPB).


**Methods**

We retrospectively reviewed our database including children who underwent cardiac surgery between January 2002 and December 2010. Four percent HA was used until 2005, and replaced by HES thereafter. Demographic, intra- and postoperative blood loss and blood components transfusion were recorded, together with the incidence of postoperative complications, and mortality. We used a propensity-matched analysis, using 13 possible confounding factors, to compare children that received intraoperatively either HES or HA. Primary objectives included the effects of both fluids on intra-operative fluid balance (difference between fluids IN and fluids OUT: efficacy), and blood loss and exposure to allogeneic blood products (safety). Secondary safety outcomes were mortality, and the incidence of postoperative renal dysfunction.

**Results**

From 1832 children reviewed, 1495 were included in the analysis. Intraoperative use of HES was associated with a less positive fluid balance. Perioperative blood loss, volume of red blood cells and fresh frozen plasma administered, and number of children transfused were also significantly lower in the HES group. No difference was observed regarding the incidence postoperative renal failure requiring renal replacement therapy, morbidity and mortality.

**Conclusions**

These results confirmed that the use of HES for volume replacement in children during cardiac surgery with CPB is as safe as human albumin. In addition, its use might be associated with less fluid accumulation. Further large studies are needed to assess if the reduction in fluid accumulation could have a significant impact on postoperative morbidity and mortality.

**Introduction**

Maintenance of normovolemia remains a major challenge during cardiac surgery with cardiopulmonary bypass (CPB). It is now accepted that both hypovolemia and fluid overload are associated with increased morbidity, and mortality [1,2]. During cardiac surgery, a relatively large amount of fluids will be administered to optimize cardiac output in the context of a drug-induced vasodilation, and to compensate for surgical blood loss [3]. In addition, the use of acellular fluids to prime the CPB will result in acute hemodilution and significantly contributes to the positive fluid balance achieved at the end of the surgery [4]. Management of hemodilution is particularly challenging in the pediatric cardiac population due to the higher ratio between the priming volume and the children’ circulating blood volume [5].

Human albumin (HA) and crystalloids remain first choices for CPB priming and volume replacement in the perioperative period of pediatric cardiac surgery [6]. Compared to crystalloids, the administration of HA in the prime decreased the intra-operative positive balance [7]. Although HA allows for the maintenance of an adequate oncotic pressure [8,9], its cost remains high, which leads physicians to look at less expensive alternatives. Third generation hydroxyethyl starches (e.g. tetrastarches) have been developed and appeared to
have interesting pharmacokinetic properties while being five times cheaper than HA. As a result of a quicker achieved optimal *in vivo* molecular weight, 6% hydroxyethyl starches (HES) 130/0.4 offers a comparable fluid volume expansion than older HES, whereas its effects on hemostasis appear less marked [10]. Recently, the safety of 6% HES 130/0.4 has been questioned in critically ill adult patients. In a prospective randomized double-blind study including about 7,000 patients, administration of 6% HES 130/0.4 has been associated with an increased need for renal replacement therapy compared to isotonic saline [11]. In another randomized double-blind trial including 804 severe septic patients, the use of balanced HES 130/0.4 was associated with an increased 90-day mortality and an increase need for renal replacement therapy compared to Ringer’s acetate [12]. Although the results of these studies lead to an intense, and sometimes emotional, debate, they should be interpreted with caution taking into account the clinical context, [13] and could not be transposed to the pediatric cardiac population.

Only few studies assessed efficacy and safety of 6% HES 130/0.4 in the pediatric population. In 2009, 6% HES 130/0.4 was compared to 4% human albumin for perioperative volume replacement therapy in a single blinded, single center, randomized trial that included 119 children undergoing cardiac surgery with CPB [14]. In this study, 6% HES 130/0.4 was associated with comparable perioperative blood loss but with a lower intraoperative fluid balance compared with 4% human albumin. These results were confirmed in a two-center, double blinded, prospective study where 6% HES 130/0.4 was compared to 5% HA in the same population (n = 61) [15]. However, both studies were not sufficiently powered to provide any firm conclusion regarding the safety of 6% HES 130/0.4 in this population.

In this large retrospective, propensity-match ed study, we assessed efficacy and safety of replacing HA with 6% HES 130/0.4 for volume replacement therapy in children undergoing cardiac surgery with CPB at our department. Our hypothesis is that HES 130/0.4 is not inferior to HA regarding our primary and secondary objectives. The primary objective for efficacy assessed the relationship between administration of 6% HES 130/0.4 and intraoperative fluid balance while primary safety objective assessed its relationship with blood loss and exposure to allogeneic blood products. As secondary objectives, we assessed the effect of 6% HES 130/0.4 on the incidence of postoperative morbidity, including the incidence of renal failure, requiring renal replacement therapy, and mortality.

### Materials and methods

After approval by our local ethic committee (Queen Fabiola Children University Hospital (QFCUH) ethic committee, CEH10/13), we retrospectively reviewed our departmental database that included all children who underwent cardiac surgery with CPB between January 2002 and December 2010. Children in a moribund state (American Society of Anesthesiology (ASA) 5), Jehovah witnesses, and those with missing data were excluded. We also excluded children < 1 month of age because these patients received primarily fresh frozen plasma (FFP) in the CPB prime, and no colloid was administered. The local ethic board waived the requirement for written informed consent due to the retrospective nature of the protocol.

During the study period, children were treated by the same team, including two experimented surgeons, three experimented anesthesiologists and two experimented ICU pediatricians. In the operating room, the anesthetic technique remains globally unchanged. Monitoring included pulse oximetry, 5-leads electrocardiogram, non-invasive arterial pressure, arterial
and central venous pressures, urinary output, and cutaneous and rectal temperature probes. Intravenous anesthesia based on midazolam, sufentanil, and rocuronium was preferred in all children, with the exception of children with univentricular physiology who underwent a cavopulmonary connection, in whom anesthesia was performed with propofol or sevoflurane, remifentanil, and atracurium. All children received cefazoline 25 mg kg\(^{-1}\), methylprednisolone 30 mg kg\(^{-1}\) after the induction of anesthesia. Antifibrinolytic agents were routinely used in our department. Aprotinin was used before 2008, and replaced thereafter by tranexamic acid. Before aortic cannulation, 4 mg kg\(^{-1}\) unfractioned heparin (UFH) was administered to reach an activated clotting time > 480 sec. Anticoagulation level was regularly checked during CPB using repeated activated clotting time (ACT) measures (ACTII monitor, Medtronic BV, Kerkrade, The Netherlands), and additional UFH boluses were given to maintain ACT > 480 sec during the whole CPB duration. At the end of CPB, protamine was administered (dose: half of the total UFH dose administrated during the whole CPB) to antagonize heparin activity. Adequate reversal was controlled using ACTII monitor comparing ACT measured in cartridges with and without heparinase (Medtronic BV, Kerkrade, The Netherlands).

The CPB circuit was primed primarily with 4% human albumin between 2002 and 2005, and with 6% hydroxyethyl starch (130/0.4) in 0.9% sodium chloride (Voluven®, Fresenius-Kabi GmbH, Bad Homburg, Germany) after this period. In addition, 20% mannitol (1.5 mL kg\(^{-1}\)), sodium bicarbonate (20 mEq L\(^{-1}\)), and UFH (50 mg L\(^{-1}\)) were added to the prime. Different models of oxygenator chosen based on body weight were used during the study period. In addition, new ‘miniaturized’ oxygenators, which require a smaller prime volume, were progressively introduced in our department since 2008.

When preparing the CPB prime, the hematocrit that will be achieved on bypass was calculated based on the volume of the prime and the estimated blood volume (EBV) of the child. Packed red blood cells (RBCs) were added in the prime when the predicted hematocrit after cardioplegia (crystalloid cold balanced solution enriched with potassium chloride 30 mmol L\(^{-1}\)) was estimated to fall below 20%. During CPB, body temperature was decreased according to the length of aortic clamp duration and the complexity of the surgery. All patients were rewarmed > 35.5 °C before weaning from CPB. After weaning, modified ultrafiltration (MUF) was used to increase hematocrit of the residual blood volume in the circuit.

For intraoperative volume replacement including CPB priming, the patients could receive up to 50 ml/kg per day of either 6% HES 130/0.4 or human albumin. For intraoperative volume replacement before or after the CPB, the amount of the 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 anesthesiologist in charge of the patient, to maintain a mean arterial pressure within the range of 50–85 mmHg. If the maximum dose of 6% HES 130/0.4 was reached, human albumin was used as rescue colloid. The use of inotropes and vasopressors was left at the discretion of the anesthesiologist and no specific algorithm was applied.

Our RBCs transfusion policy was standardized in agreement with the departments of Anesthesiology and the Pediatric Intensive Care Unit (PICU). We adopted a restrictive transfusion strategy during the study period, and this policy was maintained the same for the entire operative period and PICU stay for every patients included in this study. After separation from CPB, RBCs were transfused to maintained a hematocrit > 24% in case of
abnormal bleeding or to increase oxygen delivery in the case of persistent lactic acidosis after optimization of cardiac output with inotropes, vasoactive agents, or both. In case of abnormal bleeding, defined as a diffuse bleeding in the surgical field that could not be controlled by packing sponges, and/or application of topic hemostatic agents after adequate heparin antagonisation with protamine, FFP was administered at the dose of 15 mL kg\(^{-1}\). The same dose was repeated in case of persistent bleeding. In addition, platelets were administered in case of significant blood loss associated with a platelet count < 100 10\(^3\) μL\(^{-1}\), measured by our standard laboratory tests.

Recorded data included: age (month), preoperative weight (kg), height (cm), preoperative oxygen saturation (%), the presence of a cyanotic disease (defined as preoperative SpO\(_2\) < 90%), ASA, and RACHS (Risk Adjustment for Congenital Heart Surgery) score. This score was used to define the complexity of the surgical procedure; [16] it uses 6 categories of surgical risk, with 1 having the lower risk and 6 the highest. The incidence of preoperative cardiac failure, previous cardiac surgery with or without sternotomy was also recorded. Intraoperative characteristics, including duration of surgery, CPB and aortic cross clamp time, and minimal body temperature on bypass were recorded. The degree of hemodilution was measured in mL kg\(^{-1}\) using the ratio between the CPB prime volume (mL kg\(^{-1}\)), and the child’s estimated blood volume (EBV: mL kg\(^{-1}\)). The use of MUF, and the amount of MUF (mL kg\(^{-1}\)) were also recorded. The total fluid volume administered intraoperatively (IN) included the CPB prime volume, the cardioplegia volume, and all fluid administered with drugs and flushes of invasive pressure lines. The total output (OUT) included blood loss, urine output, and the amount of ultrafiltration. No cell savage device was used during the study period. Weighting sponges and measured surgical suction determined intraoperative blood loss, considering that irrigation volume was measured and separated from the main surgical suction. In the postoperative period, measured chest tube drainage assessed blood loss. In addition, we calculated blood loss according to the following formula, adapted from [17]:

\[
\text{Calculated blood loss (mL.kg}^{-1}\text{)} = \frac{(\text{EBV} \times \text{Hct preop}) - (\text{EBV} \times \text{Hct POD3}) + (\text{RBCs transfused up to POD3 (ml)} \times 0.7)}{\text{Patient body weight}}
\]

where

- EBV: estimated blood volume (mL)
- Hct hematocrit expressed in %
- POD3 postoperative day 3
- 0.7: mean hematocrit of the red blood cell units
- Patient body weight: preoperative body weight in kg

The incidence of RBCs, FFP, and platelet concentrates transfused intraoperatively and during the first three postoperative days was recorded. Hemoglobin level (g L\(^{-1}\)), hematocrit (%), and creatinin level (mg dL\(^{-1}\)) were systematically measured in the immediate preoperative period and on postoperative day 1, and 3. Postoperative outcome data included the incidence of surgical re-exploration for bleeding, duration of mechanical ventilation, incidence of infection, neurological complication (e.g. postoperative apparition of a neurological deficit, coma, seizures), renal replacement therapy, and in-hospital mortality.
Statistical analysis

An independent statistician blinded to the type of colloid performed the whole statistical analysis. Descriptive statistics were performed for each variables recorded in our database.

We defined ‘a priori’ 13 confounding variables to be used in the propensity-matched analysis for children included in the 2 groups: age, sex, preoperative weight, height, ASA, the presence of a cyanotic disease, history of previous cardiac surgery, history of cardiac failure, preoperative hemostatic disorder (defined as children with platelet count < 100 $10^3$ μL$^{-1}$, fibrinogen level < 100 mg dL$^{-1}$, prothrombin time (PT) and activated partial thromboplastin time (PTT) > 1.5 normal range), scheduled surgery, RACHS-1, EBV, and the administration of antifibrinolytic agent. We used a genetic matching a generalization of propensity score and Mahalanobis distance that maximizes the balance of observed covariates between treated and control groups [18]. The algorithm uses a genetic algorithm to optimize balance as much as possible given the data. The method is nonparametric and does not depend on knowing or estimating the propensity score. The Genetic matching attempts to minimize a measure of the maximum observed discrepancy between the matched treated and control covariates at every iteration of optimization. The algorithm attempts to minimize the largest observed covariate discrepancy at every step and this is accomplished by maximizing the smallest p-value at each step. The algorithm stopped when the difference between the last four solutions was small. We performed a one to one genetic matching with replacement. Last, an absolute standardized difference less than 10% was considered to support the assumption of balance between the groups because it is not affected by the sample size, unlike p-values, and it may be used to compare the relative balance of variables measured in different units [19,20]. The importance of assessing the balance of baseline covariates in the matched sample was done using standardized differences and empirical quantile-quantile (QQ) statistics. Since matched samples are no longer independent, bootstrap Kolmogorov–Smirnov (KS) tests and paired t-tests were calculated [21,22]. The mean and standard derivation (SD) obtained after matching was presented for continuous variables, while the percentage (%) was presented for categorical variables.

After matching, we used logistic regression for binary variables outcome variables and weighted linear regression (WLS) for continuous outcome variables, including the treatment group effect, the variables used for the matching score as covariate, hemofiltration and volume priming (excepted for those we observed multicollinearity with the dependent variable: hemofiltration, volume priming, ICU infection, ICU length of stay) and the weight resulting from the genetic matching. The estimators in the WLS were weighted for 1/fitted values of a first linear model. We applied a Bonferoni correction to the results: because 19 linear/logistic regression were performed, a p < 0.00263 (=0.05/19) was considered as statistically significant. Last, we performed linear mixed models to compare evolution of hemoglobin and creatinine between both groups based on multiple imputations of missing values [23].

Statistical analyses were performed with Prism 6 for Mac OS (Version 6.0d; GraphPad software inc. San Diego California USA) and the R Software version 3.0.1 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL) using the packages ‘Matching’ and ‘rgenoud’ for the match-propensity score subanalysis [18].
Results

Demographic data

From the 1832 children included in our departmental database, 1495 were included in the final analysis (Figure 1). We excluded 83 children because relevant data were missing, 82 because FFP was primarily used in the CPB prime, 7 who were in a moribund state, and 5 Jehovah witnesses. In addition, 160 children were voluntarily excluded because they already participated in one of the 2 prospective trials performed in our department, in which we compared 6% HES 130/0.4 with human albumin [14,15].

Figure 1 Flow chart.

Demographic characteristics of the studied population are reported in Table 1. Before matching, children included in the group ‘HA’ were significantly smaller (\(p = 0.03\)), had a lower preoperative body weight (\(p = 0.009\)), suffered more frequently from a cyanotic disease (\(p < 0.001\)), and experienced more often previous surgery (\(p < 0.001\)). After matching, the absolute standardized differences are clearly under 10, suggesting that we may consider the groups being equal on the selected covariates.
Table 1 Demographic characteristics of children included before and after matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Matching</th>
<th>After Matching</th>
<th>p-value</th>
<th>ASD</th>
<th>Before Matching</th>
<th>After Matching</th>
<th>p-value</th>
<th>ASD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group ‘HES’</td>
<td>Group ‘HA’</td>
<td>D</td>
<td>ASD</td>
<td>Group ‘HES’</td>
<td>Group ‘HA’</td>
<td>D</td>
<td>ASD</td>
</tr>
<tr>
<td></td>
<td>(n = 1007)</td>
<td>(n = 488)</td>
<td></td>
<td></td>
<td>(n = 1007)</td>
<td>(n = 1007)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (Month)</td>
<td>34.6 (44.1)</td>
<td>28.1 (36.1)</td>
<td>0.036</td>
<td>0.049</td>
<td>14.642</td>
<td>34.3 (44.4)</td>
<td>0.01</td>
<td>0.501</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>82.5 (28.1)</td>
<td>78.1 (25.1)</td>
<td>0.075</td>
<td>0.034</td>
<td>15.702</td>
<td>82.9 (28.3)</td>
<td>0.03</td>
<td>0.663</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>11.5 (10.2)</td>
<td>9.7 (8.9)</td>
<td>0.094</td>
<td>0.009</td>
<td>17.825</td>
<td>11.4 (9.9)</td>
<td>0.036</td>
<td>0.490</td>
</tr>
<tr>
<td>ASA</td>
<td>3.0 (0.4)</td>
<td>3.2 (0.5)</td>
<td>0.195</td>
<td>&lt;0.001</td>
<td>58.814</td>
<td>3.0 (0.4)</td>
<td>0.001</td>
<td>0.999</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>543 (54)</td>
<td>288 (59)</td>
<td>0.057</td>
<td>0.036</td>
<td>11.447</td>
<td>543 (54)</td>
<td>0.026</td>
<td>0.092</td>
</tr>
<tr>
<td>Cyanotic disease (%)</td>
<td>433 (43)</td>
<td>254 (52)</td>
<td>0.091</td>
<td>&lt;0.001</td>
<td>18.477</td>
<td>433 (43)</td>
<td>0.005</td>
<td>0.297</td>
</tr>
<tr>
<td>Re-do surgery (%)</td>
<td>164 (16.3)</td>
<td>47 (9.6)</td>
<td>0.066</td>
<td>&lt;0.001</td>
<td>18.014</td>
<td>164 (16.3)</td>
<td>0.002</td>
<td>0.655</td>
</tr>
<tr>
<td>Hemostatic disorder (%)</td>
<td>29 (2.9)</td>
<td>11.2 (2.3)</td>
<td>0.006</td>
<td>0.464</td>
<td>3.7397</td>
<td>29 (2.9)</td>
<td>0.002</td>
<td>1.157</td>
</tr>
<tr>
<td>Preop cardiac failure (%)</td>
<td>192 (19.1)</td>
<td>96 (19.7)</td>
<td>0.006</td>
<td>0.782</td>
<td>1.5409</td>
<td>192 (19.1)</td>
<td>0.011</td>
<td>0.210</td>
</tr>
<tr>
<td>Elective surgery (%)</td>
<td>996 (99)</td>
<td>473 (97)</td>
<td>0.016</td>
<td>0.038</td>
<td>15.785</td>
<td>996 (99)</td>
<td>0.002</td>
<td>0.317</td>
</tr>
<tr>
<td>RACHS-I score</td>
<td>2.5 (0.8)</td>
<td>2.6 (0.8)</td>
<td>0.100</td>
<td>0.174</td>
<td>8.8267</td>
<td>2.5 (0.8)</td>
<td>0.065</td>
<td>0.366</td>
</tr>
<tr>
<td>Antifibrinolytics (%)</td>
<td>967 (96)</td>
<td>473 (97)</td>
<td>0.003</td>
<td>0.5101</td>
<td>3.4356</td>
<td>967 (96)</td>
<td>0.001</td>
<td>0.083</td>
</tr>
<tr>
<td>Estimated blood volume (ml)</td>
<td>865 (681)</td>
<td>737 (599)</td>
<td>0.051</td>
<td>0.001</td>
<td>18.755</td>
<td>865 (681)</td>
<td>0.011</td>
<td>0.438</td>
</tr>
</tbody>
</table>

Data are expressed as mean and standard deviation (SD) or number and percentage (%). ASA: American Society of Anesthesiology score; RACHS: Risk Adjustment for Congenital Heart Surgery; preop: preoperative; ASD: Absolute standardized difference; D: D-statistic is the maximum difference in the empirical Quantile-Quantile (QQ) plot and it is sensitive to imbalance across the empirical distribution; n_o = number of observations in the original sample; n_m = number of matched observations.
Main comparisons between the two study groups are reported in Table 2. After adjustment for the confounding variables, the weight of matching and the Bonferroni correction (p-value significant if below 0.00263), CPB (p = 0.001) and surgery duration (p = 0.001) were both significantly decreased in the ‘HES’ group. The priming volume (p < 0.001), the degree of hemodilution (p < 0.001) were also lower in the “HES” group while the minimal body temperature reached on bypass was significantly lower in the ‘HA’ group.

Table 2 Comparison between groups for operative characteristics and outcomes after adjustment for confounding variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group ‘HES’ (nos = 1007)</th>
<th>Group ‘HA’ (nos = 322)</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery duration (min)</td>
<td>217.4 (67.8)</td>
<td>227.5 (98.5)</td>
<td>0.082</td>
</tr>
<tr>
<td>CPB duration (min)</td>
<td>110.8 (45.4)</td>
<td>117.6 (53.8)</td>
<td>0.013</td>
</tr>
<tr>
<td>Aortic clamping (%)</td>
<td>904 (89.8)</td>
<td>303 (94.4)</td>
<td>0.100</td>
</tr>
<tr>
<td>Min temp. on CPB (°C)</td>
<td>30.4 (2.9)</td>
<td>28.4 (3.8)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Priming volume (mL.kg$^{-1}$)</td>
<td>65.7 (34.7)</td>
<td>111.5 (54.7)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Degree of haemodilution (%)$^+$</td>
<td>80.1 (36.9)</td>
<td>136.4 (58.2)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>MUF (%)</td>
<td>921 (91.6)</td>
<td>919 (91.4)</td>
<td>0.41</td>
</tr>
<tr>
<td>MUF (mL.kg$^{-1}$)</td>
<td>29.9 (16.5)</td>
<td>31.3 (17.6)</td>
<td>0.86</td>
</tr>
<tr>
<td>Exposure to blood products (%)</td>
<td>639 (63.5)</td>
<td>801 (79.5)</td>
<td>&lt;0.001 *</td>
</tr>
<tr>
<td>Re-exploration for bleeding (%)</td>
<td>7 (0.7)</td>
<td>6 (0.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>ICU infection (%)</td>
<td>438 (43.6)</td>
<td>445 (44.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>Neurological disorder (%)</td>
<td>27 (2.7)</td>
<td>37 (3.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Postoperative cardiac assistance (%)</td>
<td>13 (1.3)</td>
<td>20 (2.0)</td>
<td>0.90</td>
</tr>
<tr>
<td>Renal replacement therapy (%)</td>
<td>11 (1.1)</td>
<td>14 (1.4)</td>
<td>0.17</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>7.5 (10.0)</td>
<td>7.0 (6.7)</td>
<td>0.41</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>19.7 (16.6)</td>
<td>20.1 (16.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>In hospital mortality (%)</td>
<td>21 (2.1)</td>
<td>7 (2.3)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

CPB: cardiopulmonary bypass; MUF: modified ultrafiltration; ICU: intensive care unit; postop: postoperative; $^+$: degree of hemodilution is presented as the mean % hemodilution with SD in parenthesis. nos = number of observations in the original sample; nm = number of matched observations. * Variable significantly different between the two groups after applying the Bonferroni’s correction.

Primary efficacy objective

A significant difference was observed for fluid administration, with higher intake (110.6 ± 44.0 for HA group vs. 87.0 ± 44.0 mL kg$^{-1}$) and output (56.1 ± 33.6 for HA group vs. 46.6 ± 25.6 mL kg$^{-1}$) in children included in the ‘HA’ group (with both p < 0.001) (Figure 2). However, the fluid balance remained more positive in the ‘HA’ group (54.1 ± 39.2 mL kg$^{-1}$ vs. 41.3 ± 30.2 mL kg$^{-1}$, p < 0.001). Modified ultrafiltration was similarly used in both groups, such as the volume of ultrafiltration which was not significantly higher in the ‘HA’ group after Bonferroni’s correction (29.9 ± 16.5 mL kg$^{-1}$ vs. 31.3 ± 17.6 mL kg$^{-1}$, p < 0.01).

Figure 2 Difference in fluid balance between groups. Red bars: ‘HA’ group; blue bars: ‘HES’ group. Data are mean ± standard deviation. # = p < 0.001.
Primary safety objective

Regarding perioperative bleeding (Figure 3), intraoperative (48.6 ± 28.6 for HA group vs. 35.8 ± 28.6 mL kg\(^{-1}\)), total (87.1 ± 77.2 for HA group vs. 70.3 ± 55.2 mL kg\(^{-1}\)), and calculated blood losses (37.9 ± 26.9 for HA group vs. 24.7 ± 19.3 mL kg\(^{-1}\)) were significantly lower in the ‘HES’ group (p < 0.001). Exposure to any blood product intraoperatively and during the first three postoperative days was significantly lower in the ‘HES’ group (Table 2), and this was essentially related to a lower exposure to RBCs (66% versus 83%; p < 0.001). The amount of RBCs and FFP transfused was also significantly lower in the ‘HES’ group (Figure 4). Interestingly, hemoglobin levels in the pre- and the immediate postoperative period were not different between the 2 groups (Table 3).

Figure 3 Comparison of perioperative blood loss between groups. Total blood loss includes the amount of blood lost intraoperatively and the blood collected in the chest tubes. Calculated blood loss has been determined according to the formula adapted from [17] (see text). Red bars: ‘HA’ group; blue bars: ‘HES’ group. Data are mean ± standard deviation. # = p < 0.001.

Figure 4 Difference in amount of blood products transfused between groups intraoperatively and during the first three postoperative days. With RBCs: Packed Red Blood Cells, FFP: Fresh Frozen Plasma, PLT: platelet concentrates. Red bars: albumin group; blue bars: ‘HES’ group. Data are mean ± standard deviation. # = p < 0.001.

Table 3 Fixed Effects comparison between groups for hemoglobin and creatinine after adjustment for confounding variables

<table>
<thead>
<tr>
<th></th>
<th>Groups</th>
<th>Preoperative</th>
<th>Postoperative day 1</th>
<th>Postoperative day 3</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g.L(^{-1}))</td>
<td>‘HES’</td>
<td>135 ± 29</td>
<td>109 ± 19</td>
<td>105 ± 18</td>
<td>0.503</td>
</tr>
<tr>
<td></td>
<td>‘HA’</td>
<td>133 ± 30</td>
<td>110 ± 22</td>
<td>107 ± 20</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg.dL(^{-1}))</td>
<td>‘HES’</td>
<td>0.35 ± 0.17</td>
<td>0.37 ± 0.18</td>
<td>0.28 ± 0.17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>‘HA’</td>
<td>0.43 ± 0.26</td>
<td>0.45 ± 0.30</td>
<td>0.41 ± 0.39</td>
<td></td>
</tr>
</tbody>
</table>

Secondary objectives

Finally, no difference was observed regarding the incidence of postoperative complication, the use of HES was not associated with an increased incidence of renal failure or requirement for renal replacement therapy (Table 2). Preoperative creatinine level was lower in the ‘HES’ group and remains lower in the immediate postoperative period (Table 3). No difference in the length of ICU stays, length of hospital stay, and mortality was reported between groups.

Discussion

In this large propensity-matched study, 6% HES 130/0.4 represented an effective and safe alternative to HA in children undergoing cardiac surgery with CPB. These results confirmed those obtained in two prospective trials [14,15], in which administration of HES 130/0.4 allowed for a significant reduction in fluid balance without any increase in blood loss, blood products transfusion requirement, and side effects. The present study included the largest cardiac pediatric population ever studied.
Regarding our primary efficacy objective, the results of our study indicated that the use of 6% HES 130/0.4 was associated with a significantly lower intraoperative fluid balance. High intraoperative fluid balance has been shown to increase ICU length of stay in adult patients undergoing coronary artery bypass graft surgery [24]. Intraoperative positive fluid could also contribute to postoperative fluid overload, which has been shown to significantly affect patient’s outcome. Following cardiac surgery, Hazle et al. observed that early postoperative fluid overload was associated with bad outcomes in infant under the age of 6 months [5]. The authors concluded that fluid overload or daily weight gain was well correlated with the incidence of acute kidney injury, which increases postoperative morbidity and mortality. In a recent large study, Hassinger et al. confirmed that early postoperative fluid overload preceded acute kidney injury and is associated with a higher morbidity in pediatric cardiac surgery patients aged between 2 weeks and 18 years old [2]. Seguin et al. reported recently that fluid overload occurs early after cardiac surgery in children and is associated with prolonged PICU length of stay and ventilation [25]. In our study, the use of 6% HES 130/0.4 might have been associated with less fluid accumulation in the early postoperative period as it may provide a better oncotic pressure that 4% albumin, which is slightly hypo-oncotic [26]. However, the results we reported could not be attributed solely to the replacement of HA by HES, as during the studied period, CPB management was modified to decrease the priming volume and therefore the degree of hemodilution achieved in our pediatric population during CPB. However, they are in accordance with those of two prospective randomized studies performed at our institution, in which the use of HES was associated with a reduction in the intraoperative fluid balance while CPB management was maintained unaltered [14,15].

Regarding the primary safety objective, our results indicated that the use of 6% HES 130/0.4 was associated with a reduced exposure to RBC and FFP transfusion in the studied population. These results did not necessarily plead for a superiority of the tetrastarches to HA as many other factors like the reduction of the degree hemodilution associated with the miniaturization of the CPB circuitries may have play a role in the reduction of blood components transfusion. However, it should be noted that both measured and calculated perioperative blood losses were significantly lower in the HES group compared to the HA group, while our restrictive transfusion policy was not modified over the studied period. These results are again in agreement with those of our previous prospective randomized studies, which reported a reduction [14] or a trend [15] to a reduction in the children exposure to allogeneic blood products. They are also in agreement with those of a recent meta-analysis [27].

Regarding our safety secondary objective, our large data set did not find an impact on morbidity or mortality with the use of HES instead of HA. Again, these results are in accordance with those of our two prospective studies, although these were not sufficiently powered to assess the safety of 6% HES 130/0.4. Our results are also in agreement with those of Sumpelmann et al. who performed a before/after study with the aim to assess the incidence of adverse reaction associated with the use of 6% HES 130/0.42 [28]. In this study including 1130 children undergoing surgery and exposed to 6% HES 130/0.42, the authors did not report any adverse reaction, while only non-clinically relevant changes in metabolic parameters (plasma chloride ion concentration, excess base) was observed. Recent systematic reviews and meta-analyses have confirmed that the use of 6% HES 130/0.4 is not associated with a deleterious effect on postoperative morbidity and mortality [13,27,29,30], in contrast to what has been observed in the critically ill patients [31-33]. Our results are also in line with a recent study, which reported comparable efficacy and safety profile between HA and HES in adults patients undergoing cardiac surgery [34]. Although the requirement for RRT is
usually infrequent in children undergoing cardiac surgery, the maximal postoperative creatinine level was not increased in children who received HES, and was significantly lower than in patients who received HA. Although these results should be interpreted knowing the limitations described below, our study did not reported any signal of potential harmful effect associated with HES administration in children undergoing cardiac surgery.

The result of our study should be interpreted knowing the limitation of this work. This study is not a randomized controlled trial, and although powerful adjustment methods have been used, the probability of unrecognized confusion bias still persists. We used propensity-matched analysis performed using 13 variables defined, ‘a priori’, as possible factors that could influence the difference between both study groups. Although the choice of these 13 factors could be extensively discussed, we used both the most relevant demographic and clinical parameters that could have influenced the repartition between both study groups.

Aprotinin was withdrawn from the market after the publication of the BART study [35]. We therefore switched from aprotinin to tranexamic acid in 2008 and this might have influenced our results regarding perioperative blood loss. However, according to a recent meta-analysis, there is no prospective study, which as directly compared aprotinin to tranexamic acid in pediatric cardiac surgery [36]. In a recent retrospective analysis including more than 22,000 patients, Pasquali et al. reported that, compared to aprotinin, tranexamic acid was associated with significantly reduced mortality and bleeding requiring surgical intervention [37]. However, the statistical analysis for our different outcome parameters was adjusted for the type of antifibrinolytic agent used. We therefore believe that the switch from aprotinin to tranexamic acid in 2008 has not significantly influenced our results.

In this study, we voluntarily avoid adjusted analysis with the year of the surgery because this parameter would co-vary with the change from HA to 6% HES 130/0.4, which would bias the results of our regression analyses. Although we performed the propensity-matched analysis based on 13 relevant parameters, we agree that the results we observed could not be attributed solely to the different colloids administered. The changes in our priming strategy should be considered as part of a multimodal approach aiming to improve children’s blood management strategy, which includes the adoption of a restrictive transfusion policy.

**Conclusion**

In conclusion, the results of this large propensity-matched analysis confirmed the results obtained in 2 previous prospective randomized trials showing that the use of 6% HES 130/0.4 for volume replacement in children undergoing cardiac surgery with CPB was an effective and safe alternative to human albumin. Its use was associated with a less positive intraoperative fluid balance, which might have an impact on early postoperative fluid overload. Further large studies are needed to assess if the reduction in intraoperative fluid accumulation could have a significant impact on postoperative morbidity and mortality.

Due to the higher cost of human albumin, 6% HES 130/0.4 could be considered as a safe and cost-effective alternative in pediatric cardiac surgery.
Key messages

- The use of hydroxyethyl starches for volume replacement in children undergoing cardiac surgery with CPB appears as safe as human albumin.
- The use of hydroxyethyl starches might be associated with less fluid accumulation, which might have a significant impact on postoperative morbidity and mortality.

Abbreviations

ACT, activated clotting time; ASA, American Society of Anesthesiology; CPB, cardiopulmonary bypass; EBV, estimated blood volume; FFP, fresh frozen plasma; HA, human albumin; HES, hydroxyethyl starches; MUF, modified ultrafiltration; PICU, pediatric intensive care unit; PT, prothrombin time; RBC, red blood cells; UFH, unfractioned heparin; APTT, activated partial thromboplastin time.

Competing interests

PVdL: In the past 5 years, Prof. Van der Linden has received fees for lectures and consultancies from Fresenius Kabi GmbH, and Janssen-Cilag SA, Belgium. Other authors have no conflict of interest. Other authors have no conflict of interest.

Authors’ contributions

PVdL and DF contributed to the conception and design of the study and drafted the manuscript. MD, CVL, CST and CST recorded the data and contributed with PVdL and DF to interpretation of data and revised the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Acknowledgement

This work is attributed to, and was solely supported by, the Department of Anesthesiology, University Hospital Brugmann and Queen Fabiola Children’s University Hospital, Free University of Brussels, Brussels, Belgium. The authors acknowledge Jean-François Fils, independent statistician, who performed the statistical analysis. AW and DF received personal funding to support research time from the Belgian Kids Fund, http://www.belgiankidsfund.be.

References


Cardiac surgery with CPB
N=1,832

Excluded: N=337
Jehovah witness: 5
ASA 5: 7
Missing data: 83
FFP: 82
RCTs: 160

Children included
N=1,495

Group ‘HES’
N=1,007

Group ‘HA’
N=498