의학박사 학위논문

The effect of 6% hydroxyethyl starch (130/0.4) on acute kidney injury in paediatric cardiac surgery

A prospective, randomised trial

심장 수술을 받는 어린이에서 Hydroxyethyl starch 사용이 수술 후 급성 신장 손상 발생에 주는 영향

전향적 무작위배정비교임상시험

2018 년 2 월

서울대학교 대학원

의학과 마취통증의학 전공

오 혜 원

A thesis of the Degree of Doctor of Medical Science

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이 논문을 의학박사 학위논문으로 제출함

2018 년 2 월

서울대학교 대학원

의학과 마취통증의학 전공

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오혜원의 의학박사 학위논문을 인준함

2018 년 2 월

위 원 장 (인)

부 위 원 장 (인)

위 원 (인)

위 원 (인)

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A prospective, randomised trial

by

Hye-Won Oh

(Directed by Jin-Tae Kim, M.D., Ph.D.)

A thesis submitted to the Department of Anesthesiology in partial fulfillment of the requirement of the Degree of Doctor of Medical Science at Seoul National University College of Medicine

February 2018

Approved by Thesis Committee:

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ABSTRACT

We have evaluated the effect of a colloid solution on acute kidney injury (AKI) in paediatric cardiac surgery. A total of 195 patients were randomly divided into an hydroxyethyl starch (HES) group and a control group. In the HES group, 6% HES 130/0.4 (Volulyte®) was used as the primary fluid for volume resuscitation but was limited to 30 ml.kg-1. In the control group, only crystalloid fluid was used during the peri-operative period. The incidence of AKI, peri-operative transfusion, clinical outcomes and laboratory data were compared. The incidence of AKI determined by Paediatric Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE) and Acute Kidney Injury Network (AKIN) criteria were no different between the two groups (HES group 40.8% vs control group 30.0%; p = 0.150 using pRIFLE; 19.6% vs. 21.1%, P = 0.602 using AKIN). There were no differences in clinical outcomes such as mortality, major adverse events, length of intensive care unit stay or duration of mechanical ventilation. Clotting time on the external TEMogram was more prolonged, and clot firmness after 10 min and maximal clot firmness on the fibrinogen TEMogram were shorter in the HES group compared with the control group after sternal closure. However, there was no difference in the transfusion requirement between the two groups. Patients with AKI had worse clinical courses than those without AKI. We conclude that intra-operative use of 6% HES 130/0.4 up to 30 ml.kg-1 was not inferior to crystalloid in terms of the incidence of AKI in paediatric cardiac patients.

Keywords: congenital heart disease; crystalloid vs colloid; paediatrics; renal failure; cardiopulmonary bypass; surgery

Student number: 2015-30595

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INTRODUCTION

Colloid solutions are used for volume resuscitation in order to maintain intravascular volume and reduce transfusion requirements. However, previous studies have questioned the efficacy and safety of colloids [1-3]. In critically ill adults, hydroxyethyl starch (HES) 130/0.42 has been associated with acute kidney injury (AKI) and an increased requirement for renal replacement therapy [2, 4]. The Surviving Sepsis Campaign guidelines recommend crystalloid solutions for initial resuscitation rather than HES [5]. However in one study, critically ill patients who received colloids, including gelatin, dextrans, HES and albumin for resuscitation demonstrated a lower 90-day mortality compared with those who received crystalloids [6]. Additionally, it is unclear whether HES is harmful if limited to peri-operative use [7]. More evidence is required to determine the peri-operative effect of colloids in hypovolaemic patients and there are limited data regarding intra-operative use in children.

Recent advances in surgical techniques and anaesthetic care have improved outcomes in children with congenital heart disease. However, the incidence of postoperative acute kidney injury (AKI) is between 27% and 50% [8-10], with a 20%–79% mortality [11]. Known AKI risk factors after paediatric cardiac surgery are young age, surgical complexity, prolonged cardiopulmonary bypass (CPB) times and reduced pre-operative haemoglobin levels [11, 12]. Data regarding the effect of a new colloid solution, 6% HES 130/0.4 (Volulyte®, Fresenius Kabi GmbH, Bad Homgurg, Germany) on AKI after paediatric cardiac surgery are limited. We decided to determine whether there was an association between intra-operative HES 130/0.4 and postoperative AKI in paediatric cardiac patients. We also wanted to compare HES 130/0.4 with a crystalloid solution on blood loss and other clinical outcomes.

METHODS

Following local research ethics committee approval, children aged less than 7 years, of ASA physical status 1-3, undergoing cardiac surgery with cardiopulmonary bypass between November 2015 and 2016, were enrolled. The day before surgery, a staff member met with each child's parent or guardian, explained the study protocol and obtained written informed consent. Exclusion criteria were pre-operative creatinine values exceeding 1.5 $mg.dl^{-1}$, a history of renal replacement therapy, liver function abnormality (aspartate transaminase > 40 $units.l^{-1}$, alanine aminotransferase > 40 $units.l^{-1}$), diabetes mellitus, allergy or coagulation disorder (platelets < 150,000 $.mm^{-3}$, prothrombin time > 70% of control, activated partial thromboplastin time > 45 s, fibrinogen < 100 $mg.l^{-1}$).

Patients were randomly allocated to one of two groups, HES or control group in a ratio of 1:1. A stratified randomisation assignment was used to create group assignment for surgical complexity-based sub-group analysis. The surgery was categorised using Risk Adjustment for Congenital Heart Surgery (RACHS) [13]. Random allocation sequence was performed by a research assistant who prepared coded and sealed opaque envelopes. The assistant then opened the envelopes after enrolment.

Patients were monitored according to Anaesthetists of Great Britain and Ireland (AAGBI) guidelines, intravenous access was obtained and anaesthesia induced with atropine (0.02 $mg.kg^{-1}$), thiopental sodium (5 $mg.kg^{-1}$), rocuronium (1.2 $mg.kg^{-1}$), and fentanyl (10 $\mu g.kg^{-1}$) and was maintained using a continuous infusion of midazolam, sufentanil and vecuronium. In the HES group, 6% HES 130/0.4 (Volulyte®) in a balanced solution was primarily used for volume resuscitation and 5 $ml.kg^{-1}$ 6% HES 130/0.4 was added to the pump prime volume. The volume of 6% HES 130/0.4 was limited to a total of 30 $ml.kg^{-1}$ and crystalloid (Plasma solution A; CJ, Seoul, Korea) was infused when additional intravascular volume expansion was required. In the control group crystalloid only was used. The volume of crystalloid added to the pump prime was determined by the CPB circuit volume and haematocrit. After

sternotomy, and following venous and aortic cannulation, heparin 300 units.kg^{-1} was administered in order to achieve an activated clotting time of 450 s. Cardiopulmonary bypass was instituted using non-pulsatile flow and varying degrees of hypothermia depending on the surgical procedure. A haematocrit of 25–28% was maintained during CPB and blood was added if necessary. Bypass flow rate was maintained at 120–170 ml.kg^{-1}.min^{-1}.

Transfusion criteria were the same in both groups; packed red cells were transfused when the haemoglobin was < 80 g.l^{-1} in non-cyanotic children and < 100 g.l^{-1} in cyanotic children. Additional red cells were transfused when the cerebral oximeter value (INVOS®; Somanetics Corp., Troy, MI, USA) decreased below the baseline level despite correction for other factors including cardiac output or pump flow, perfusion pressure, partial pressures of arterial carbon dioxide and oxygen as well as aortic and venous cannulae positions. After separation from CPB and protamine administration, fresh frozen plasma, cryoprecipitate or platelet transfusions were administered based on ROTEM® (TEM International GmbH, Munich, Germany) data; a fibrinogen TEMogram (FIBTEM with platelet-inhibiting cytochalasin D added to discern fibrin polymerisation and external TEMogram (EXTEM with calcium and tissue factor added to evaluate the extrinsic pathway, were obtained. Fresh frozen plasma or cryoprecipitate were transfused if clot firmness after 10 min (A10) on the EXTEM was > 35 mm and maximum clot firmness (MCF) on the FIBTEM was ≤ 5 mm; platelets were administered if EXTEM A10 was ≤ 35 mm and FIBTEM MCF was > 5 mm and both fresh frozen plasma or cryoprecipitate and platelets were given if the EXTEM A10 was ≤ 35 mm and FIBTEM MCF was ≤ 5 mm.

Heparin reversal was confirmed using the activated clotting time. EXTEM and FIBTEM were measured at two time-points for each patient: after protamine infusion and following sternal closure. Postoperatively, patients were transferred to the paediatric intensive care unit and their lungs were mechanically ventilated. Postoperative fluids were given according to local policy. Laboratory data, transfusion amount, volume expansion, urine output and blood loss were evaluated up to postoperative day 7. Intra-operative and postoperative vaso-active inotropic scores

were calculated as follows: dopamine dose ($\mu g.kg^{-1}.min^{-1}$) + dobutamine dose ($\mu g.kg^{-1}.min^{-1}$) + 100 × adrenaline dose ($\mu g.kg^{-1}.min^{-1}$) + 10 × milrinone dose ($\mu g.kg^{-1}.min^{-1}$) + 10,000 × vasopressin dose ($U.kg^{-1}\ min^{-1}$) + 100 × noradrenaline dose ($\mu g.kg^{-1}.min^{-1}$) [14].

The primary outcome was the incidence of AKI after cardiac surgery. We used Paediatric Risk, Injury, Failure, Loss, and End-stage renal disease (pRIFLE) criteria [15] and Acute Kidney Injury Network (AKIN) classifications [16]. The pRIFLE classifications are as follows: risk, estimated glomerular filtration rate (eGFR) decreased by 25%; injury, eGFR decreased by 50%; failure, eGFR decreased by 75% or eGFR < 35 $ml.min^{-1}$ per 1.73 m^2. The eGFR was calculated using revised Schwartz formula as follows; creatinine clearance = (0.413×height) serum $creatinine^{-1}$ [17]. The AKIN classifies AKI into three stages: stage 1, increase in plasma creatinine of 0.3 $mg.dl^{-1}$ or to 150–200% of baseline; stage 2, increase in plasma creatinine to 200–300% of baseline; and stage 3, increase in plasma creatinine to > 300% (> threefold) of baseline (increase of at least 0.5 $mg.dl^{-1}$), postoperative plasma creatinine concentration of 4.0 $mg.dL^{-1}$, or need for postoperative renal replacement therapy.

Clinical outcomes including major adverse events, duration of mechanical ventilation of the lungs, length of intensive care unit (ICU) and hospital stays, and mortality were assessed and compared between the groups. Major adverse events were defined as cardiac arrest, re-sternotomy due to haemodynamic instability, extracorporeal membrane oxygenation support, significant arrhythmia requiring treatment, cerebral haemorrhage or infarct and pulmonary complications.

The sample size was calculated for the analysis of binary outcome for non-inferior test. According to previous studies the incidence of AKI after paediatric cardiac surgery varies between 9% and 42% [9, 18, 19]. Therefore, we assumed that the incidence of AKI would be 15% in both the HES and the control groups. An equivalence margin (non-inferiority limit) was defined as 13%. We set a power of 0.8 and a type I error of 0.05 for the non-inferiority test. The required sample size was 94 patients per group and we decided to include 200 patients in order to allow for a dropout rate of 8%.

Data normality was tested using the Kolmogorov–Smirnov test. The Chi-squared test was used to test categorical data significance, and Fisher's exact test was used when > 20% of the cells had expected counts less than five. Student's t test or the Mann–Whitney rank-sum test was used to test continuous data significance.

Subgroup analysis was performed according to degree of classification, age and RACHS. All data were analysed using SPSS for Windows (version 21.0; SPSS, Inc., Chicago, IL, USA) and a $p < 0.05$ was considered statistically significant.

RESULTS

Two hundred patients were randomised into one or the other group. The data for five patients, two in the HES group and three in the control group, were excluded from analysis and the data from the remaining 195 patients were analysed (Fig 1). Baseline patient characteristics and intra-operative data are shown in Tables 1 and 2. There were no significant differences in pre-operative laboratory data, CPB duration or anaesthesia duration between the groups. Mean (SD) Intra-operative urine output was 22.6 (14.3) $ml.kg^{-1}.h^{-1}$; in the HES group compared with 31.5 (16.8) in the control group, 95% confidence interval [CI] of difference: 4.6–13.4 ml kg^{-1} h^{-1}; $p < 0.001$. Intra-operative total fluid amount ($p = 0.127$), amount of ultrafiltration during CPB ($p = 0.32$) and immediate postoperative weight gain were the same in both groups ($p = 0.071$).

The ROTEM data demonstrated differences in coagulation profiles between the groups. Mean (SD) EXTEM clotting time was 118.4 (30.4) s in the HES group compared with 105.8 (43.8) s in the control group following protamine administration (95%CI -23.0 to -1.1 s; $p = 0.032$) and after sternal closure mean (SD) was 83.6 (19.3) s compared with 92.0 (19.6), 95%CI -14.0 to -2.8 s; $p = 0.004$ (Table 3). The mean (SD) FIBTEM MCF after sternal closure was significantly less in the HES group than in the control group, 7.0 (3.7) vs. 8.1 (3.7) mm, 95%CI 4.6–13.4 mm; $p = 0.037$. Total intra-operative transfusion volumes were the same for both groups.

Table 4 shows the postoperative characteristics and clinical outcomes. Acute kidney injury incidences assessed using pRIFLE and AKIN classifications were 35.9% and 21.0%, respectively. Most patients had low-grade AKI; there was no significant difference between the groups in terms of AKI incidence with either classification between the groups (40.8% in the HES group compared with 30.9% in the control using pRIFLE, $p = 0.150$, and 21.1% in the HES group compared with 19.6% in the control group using AKIN, $p = 0.602$). There were no significant differences between the groups in terms of postoperative transfusion, laboratory data, duration of

mechanical ventilation of the lungs, lengths of ICU or total hospital stays, and mortality did not differ between the groups.

Table 5 shows the clinical outcome comparisons between patients with and without AKI. When AKI occurred and was evaluated using pRIFLE criteria, children with AKI had longer durations of mechanical ventilation and lengths of ICU and hospital stays compared with those without AKI. The incidence of major adverse events was significantly higher in children with AKI compared with those without (22.9% vs. 9.6%, $p = 0.011$). When AKI was assessed using the AKIN classification, there were no differences in the duration of mechanical ventilation or lengths of ICU and hospital stays between groups, however, the incidence of major adverse events was higher in patients with AKI compared with those without (35.7% vs. 8.5%, $p < 0.001$).

Subgroup analysis

AKI classification low grade vs. high grade

Table 6 shows the postoperative AKI incidence by each classification after cardiac surgery for patients in the HES group and the control group. In this subgroup analysis, both classification was divided into two larger stages; injury and failure combined in pRIFLE, stage 2 and 3 combined in AKIN. There was still no significant difference between the groups ($p = 0.134$ using pRIFLE and $p = 0.951$ using AKIN).

Infants vs. children older than 1 year

We performed subgroup analysis for infants and children older than 1 year.

The clinical outcome was worse in infants than in children older than 1 year in terms of mechanical ventilation duration, length of ICU stay and incidence of major adverse events. (Table 7).

Table 8 shows the AKI incidence between the HES and control groups in both infants and children older than 1 year respectively. There were no differences in AKI incidences assessed using pRIFLE and AKIN classifications between the HES

group and the control group in children older than 1 year. In neonates, this result was similar when AKIN classification was used for classification. However, there was significant difference in AKI incidence assessed using pRIFLE classification between the HES group and the control group (p = 0,005).

We compared postoperative clinical outcome between the HES and control groups in infants because there was a difference in AKI incidence classified using pRIFLE classification between the two groups. However, we found no difference in clinical outcomes between the HES and control groups in infants. (Table 9)

RACHS 1, 2 vs. RACHS 3, 4, 5

As the number of patients in each RACHS score is distributed diversely according to Table 1, score 1 and 2 were bound as one group and score 3, 4 and 5 were bound as another for further evaluation. The postoperative outcomes in RACHS score 1 or 2 group and RACHS score 3, 4 or 5 group were overall different (Table 10). The patients with lower RACHS score had better clinical outcomes.

Table 11 shows the AKI incidence among these RACHS score subgroups by means of two AKI classification. Most of the patients were distributed in score 1 or 2 in both the HES and control group. The only shown significant difference between the groups was AKI classified with pRIFLE in patients with RACHS score 1 or 2. The incidence was 32 (32.7%) in the HES group compared to 21 (21.6%) in the control group, p = 0.03.

Table 12 represents the postoperative outcomes after cardiac surgery in patients with RACHS score 1 or 2 between the two groups. The HES group had significantly longer mechanical ventilation duration; 53.5 (68.7) than in the control group; 35.5 (32.0), otherwise both groups were similar.

Table 1. Baseline characteristics of patients in the hydroxyethyl starch (HES) and control groups. Values are median (IQR [range]), number (proportion) or mean (SD).

	HES group n=98	Control group n=97
Age; years	0.4 (0.2-2.1 [0.0-6.8])	0.5 (0.2-1.2 [0.0-6.7])
Height; cm	65.2 (58.1-85.1 [43.5-120.8])	65.1 (59.9-74.4 [47.0-133.0])
Weight; kg	6.8 (4.6-10.4 [2.0-40.5])	6.9 (5.4-9.0 [3.6-35.7])
Sex; male	53 (54%)	53 (55%)
RAHCS score		
1	13 (13%)	12 (12%)
2	56 (57%)	61 (62%)
3	22 (22%)	16 (16%)
4	7 (7%)	9 (9%)
5	0 (0%)	1 (1%)
Pre-operative laboratory data		
Albumin; $g.dl^{-1}$	4.3 (0.3)	4.3 (0.4)
Creatinine; $\mu mol.L^{-1}$	29.1 (9.7)	29.1 (9.7)
GFR; $ml.min^{-1}.1.73\ m^{-2}$	99.7 (32.4)	97.9 (33.8)
PT-INR	1.08 (0.09)	1.10 (0.15)
aPTT; s	37.7 (6.1)	38.2 (7.1)

RACHS, Risk Adjustment for Congenital Heart Surgery; GFR, Glomerular filtration rate; PT-INR, prothrombin time-international normalised ratio; aPTT, activated partial thromboplastin time.

Table 2. Intra-operative data for patients in the hydroxyethyl starch (HES) and control groups. Values are mean (SD) or median (IQR [range]).

	HES group n=98	Control group n=97	95% CI of differences	p value
Anaesthesia time; min	349.9 (101.1)	347.1 (86.1)	-30.1 to 23.2	0.836
Operative time; min	298.6 (95.7)	295.7 (86.3)	-29.2 to 23.4	0.825
CPB time; min	139.7 (56.0)	144.7 (56.2)	-10.7 to 21.1	0.529
ACC time; min	77.8 (38.8)	85.5 (52.8)	-5.1 to 21.2	0.250
Ultrafiltration during CPB; $ml.kg^{-1}$	36.6 (18.4)	34.2 (15.3)	-7.2 to 2.4	0.320
Intraoperative laboratory data				
Minimum haemoglobin; $g.dl^{-1}$	8.4 (1.1)	8.5 (1.3)	-1.7 to -0.5	0.333
Maximum glucose; $mmol.L^{-1}$	10.4 (2.5)	10.2 (2.5)	-0.9 to 0.5	0.274
Minimum glucose; $mmol.L^{-1}$	6.1 (1.3)	5.9 (1.4)	-0.6 to 0.2	0.272
Intra-operative urine output; $ml.kg^{-1}.h^{-1}$	22.6 (14.3)	31.5 (16.8)	4.6 to 13.4	0.000
Urine output during CPB; $ml.kg^{-1}.h^{-1}$	18.2 (11.3)	19.6 (13.3)	-2.0 to 4.9	0.411
Intra-operative blood loss; $ml.kg^{-1}$	17.0 (25.0)	16.3 (22.5)	-7.4 to 6.0	0.835
Intra-operative crystalloid; $ml.kg^{-1}$	25.1 (27.5)	47.4 (46.2)	11.6 to 33.1	0.000
Intra-operative HES; $ml.kg^{-1}$	14.0 (6.2)	N/A	-15.4 to -12.3	0.000
Intra-operative total fluid; $ml.kg^{-1}$	39.0 (30.6)	47.6 (46.0)	-2.5 to 19.7	0.127
Intra-operative transfusion; units				
Packed red cells	0.5 (0.3-0.9 [0.0-2.8])	0.5 (0.3-0.7 [0.0-3.6])		0.083
Fresh frozen plasma	0.3 (0.0-1.0 [0.0-2.5])	0.4 (0.0-1.0 [0.0-2.0])		0.880
Platelet concentrate	1.0 (0.0-1.0 [0.0-10.0])	1.0 (0.0-1.0 [0.0-12.0])		0.796
Cryoprecipitate	0.0 (0.0-0.0 [0.0-0.2])	0.0 (0.0-0.0 [0.0-0.0])		0.320
Intra-operative maximum VIS	12.3 (8.1)	11.3 (6.6)	-3.1 to 1.1	0.329
Immediate postoperative weight gain; kg	0.0 (-0.3-0.2 [-1.9-1.5])	0.0 (-1.0-0.2 [-0.9-2.4])		0.071

CPB, cardiopulmonary bypass; ACC, aortic cross-clamp time; N/A, not applicable; VIS, vaso-active inotropic score.

Table 3. Rotational thromboelastometry values after weaning from cardiopulmonary bypass for patients in the hydroxyethyl starch (HES) and control groups. Values are mean (SD).

	HES group n=98	Control group n=97	95% CI of differences	p value
After protamine administration				
EXTEM				
CT; s	118.4 (30.4)	105.8 (43.8)	-23.0 to -1.1	0.032
CFT; s	227.8 (107.9)	200.7 (97.6)	-55.2 to 3.6	0.085
Alpha angle; °	53.8 (8.9)	56.1 (9.5)	-0.3 to 5.0	0.081
A10; mm	36.1 (8.0)	37.7 (8.4)	-7.7 to 4.1	0.181
MCF; mm	46.0 (7.2)	47.8 (9.3)	-0.5 to 4.1	0.126
FIBTEM				
CT; s	340.5 (735.3)	176.4 (548.7)	-349.2 to 20.9	0.082
A10; mm	4.8 (2.4)	6.0 (3.0)	0.4 to 2.1	0.002
MCF; mm	5.8 (7.1)	6.5 (3.7)	-1.0 to 2.3	0.404
After sternal closure				
EXTEM				
CT; s	92.0 (19.6)	83.6 (19.3)	-14.0 to -2.8	0.004
CFT; s	154.1 (49.5)	151.6 (50.8)	-16.9 to 12.0	0.737
Alpha angle; °	62.3 (9.6)	62.1 (6.3)	-2.5 to 2.2	0.932
A10; mm	42.9 (7.1)	43.1 (5.9)	-1.7 to 2.1	0.832
MCF; mm	52.5 (6.4)	52.6 (6.2)	-1.8 to 1.9	0.960
FIBTEM				
CT; s	144.1 (408.3)	122.5 (446.1)	-144.7 to 101.3	0.728
A10; mm	6.4 (3.1)	7.4 (3.1)	-1.0 to 1.8	0.040
MCF; mm	7.0 (3.7)	8.1 (3.7)	0.1 to 2.2	0.037

Reference ranges:

External TEMogram (EXTEM) CT (42-74), CFT (46-148), Alpha angle (63-81), A10 (43-65), MCF (49-71); Fibrinogen TEMogram (FIBTEM) CT (39-76), A10 (9-24), MCF (9-25) in adults [48].

EXTEM CT (37-97), CFT (30-146), Alpha angle (64-84), A10 (43-65), MCF (46-74); FIBTEM A10 (5-24), MCF (6-25) in children (0-5 years) [49].

CT, clotting time; CFT, clot formation time; A10, clot firmness after 10 minutes; MCF, maximum clot firmness.

Table 4. Postoperative characteristics and outcomes after cardiac surgery for patients in the hydroxyethyl starch (HES) and control groups. Values are median (IQR [range]), mean (SD) or number (proportion).

	HES group n=98	Control group n=97	95% CI of differences	p value
Postoperative transfusion; units				
Packed red cells	0.4 (0-0.7 [0-2.1])	0.3 (0.1-0.4 [0-2.0])		0.572
Fresh frozen plasma	0.1 (0-0.5 [0-5.0])	0.1 (0-0.4 [0-9.8])		0.792
Platelet concentrate	0 (0-0 [0-6.3])	0 (0-0 [0-9.3])		0.423
Cryoprecipitate	0 (0-0 [0-6.0])	0 (0-0 [0-2.3])		0.777
Postoperative laboratory data				
Minimum Hb; $g.dl^{-1}$	9.9 (1.1)	10.0 (1.2)	-0.2 to 0.5	0.329
Maximum PT-INR	1.43 (0.26)	1.38 (0.27)	-0.08 to 0.02	0.197
Maximum aPTT; sec	48.4 (16.2)	44.7 (17.8)	-8.7 to 1.2	0.140
Minimum fibrinogen; $mg.dl^{-1}$	151.8 (40.9)	148.0 (38.3)	-15.1 to 7.3	0.498
Minimum platelet; $\times 10^3\ \mu l^{-1}$	167.5 (66.4)	155.6 (53.4)	-29.0 to 5.1	0.169
Maximum Creatinine; $\mu mol.L^{-1}$	38.01 (15.91)	35.36 (16.80)	-7.1 to 1.8	0.367
Maximum Glucose; $mmol.L^{-1}$	13.0 (4.3)	13.4 (5.2)	-0.9 to 1.8	0.498
Minimum Glucose; $mmol.L^{-1}$	7.2 (1.7)	7.3 (2.0)	-0.5 to 0.6	0.831
Clinical outcomes				
MV duration; h	57.6 (76.2)	53.8 (73.9)	-25.0 to 17.4	0.724
Length of ICU stay; h	117.3 (204.3)	97.4 (113.6)	-66.7 to 26.8	0.402
Length of hospital stay; days	14.2 (12.6)	12.2 (8.6)	-5.1 to 1.0	0.187
Major adverse events	17 (17.3%)	11 (11.3%)		0.232
Mortality	1 (1%)	1 (1%)		0.994
Patients with AKI				
PRIFLE classification	40 (40.8%)	30 (30.9%)		0.150
Risk	27 (27.6%)	25 (25.8%)		
Injury	5 (5.1%)	2 (2.1%)		
Failure	8 (8.2%)	3 (3.1%)		
AKIN classification	23 (21.1%)	19 (19.6%)		0.602
Stage 1	13 (13.3%)	10 (10.3%)		
Stage 2	3 (3.1%)	1 (1.0%)		
Stage 3	7 (7.1%)	8 (8.2%)		

Hb, haemoglobin; PT-INR, prothrombin time-international normalized ratio; aPTT, activated partial thromboplastin time; MV, mechanical ventilation; ICU, intensive care

unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 5. Postoperative outcomes after cardiac surgery in patients with AKI compared with those without AKI. Values are number (proportion) or mean (SD).

	Patients with AKI	Patients without AKI	95% CI of differences	p value
pRIFLE classification				
Number of patients	70 (35.9%)	125 (64.1%)		
MV duration; h	66.5 (72.8)	36.8 (42.3)	-51.2 to -8.1	0.000
Length of ICU stay; h	135.9 (241.9)	76.4 (96.4)	-109.6 to -9.4	0.020
Length of hospital stay; d	15.3 (12.7)	11.6 (9.8)	-7.8 to -1.1	0.038
Major adverse events	16 (22.9%)	12 (9.6%)		0.011
Mortality	1 (1.4%)	1 (0.8%)		0.676
AKIN classification				
Number of patients	41 (21.0%)	152 (79.0%)		
MV duration; h	52.9 (44.7)	44.8 (59.6)	-33.7 to 17.4	0.531
Length of ICU stay; h	165.6 (342.4)	83.5 (101.0)	-230.9 to 66.8	0.266
Length of hospital stay; d	15.5 (16.2)	12.4 (9.9)	-7.9 to 1.7	0.206
Major adverse events	15 (35.7%)	13 (8.5%)		0.000
Mortality	1 (2.4%)	1 (0.7%)		0.325

MV, mechanical ventilation; ICU, intensive care unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 6. Difference in postoperative acute kidney injury incidence between the hydroxyethyl starch (HES) and control groups. Values are median (IQR [range]), mean (SD) or number (proportion).

	HES group n=98	Control group n=97	95% CI of differences	p value
Patients with AKI				
PRIFLE classification	40 (40.8%)	30 (30.9%)		0.134
Risk	27 (27.6%)	25 (25.8%)		
Injury + Failure	13 (13.3%)	5 (5.2%)		
AKIN classification	23 (21.1%)	19 (19.6%)		0.951
Stage 1	13 (13.3%)	10 (10.3%)		
Stage 2 + 3	10 (10.2%)	9 (9.3%)		

AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 7. Difference in postoperative outcomes in patients between under age 1 and over age 1. Values are number (proportion) or mean (SD).

	Patients under age 1	Patients over age 1	95% CI of differences	p value
Number of patients	137 (70.3%)	58 (29.7%)		
MV duration; h	69.0 (83.0)	24.3 (35.1)	22.4 to 67.0	0.000
Length of ICU stay; h	131.4 (188.9)	50.6 (57.9)	30.8 to 130.7	0.002
Length of hospital stay; d	13.4 (9.4)	12.7 (13.7)	-2.6 to 4.1	0.668
Major adverse events	15 (10.9%)	0 (0.0%)		0.006
Mortality	2 (1.5%)	0 (0.0%)		1.000

MV, mechanical ventilation; ICU, intensive care unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 8. Difference in postoperative acute kidney injury incidence between the hydroxyethyl starch (HES) and control groups sorted by age. Values are median (IQR [range]), mean (SD) or number (proportion).

	HES group n=98	Control group n=97	95% CI of differences	p value
Age				
Under 1 year old				
AKIN classification	64 (65.3%)	71 (73.2%)		0.181
AKI (-)	21 (21.4%)	16 (16.5%)		
AKI (+)	43 (43.9%)	55 (56.7%)		
pRIFLE classification	64 (65.3%)	71 (73.2%)		0.005
AKI (-)	26 (26.5%)	46 (47.4%)		
AKI (+)	38 (38.8%)	25 (25.8%)		
Over 1 year old				
AKIN classification	34 (34.7%)	26 (26.8%)		1.000
AKI (-)	32 (32.7%)	24 (24.7%)		
AKI (+)	2 (2.0%)	2 (2.1%)		
pRIFLE classification	34 (34.7%)	26 (26.8%)		0.222
AKI (-)	32 (32.7%)	21 (21.6%)		
AKI (+)	2 (2.0%)	5 (5.2%)		

AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 9. Difference in postoperative outcomes between the hydroxyethyl starch (HES) and control groups in patients under age 1. Values are number (proportion) or mean (SD).

	HES group n=73	Control group n=64	95% CI of differences	p value
Patients under age 1				
MV duration; h	75.3 (85.6)	63.5 (80.8)	-40.0 to 16.5	0.411
Length of ICU stay; h	152.9 (242.4)	112.6 (123.2)	-106.9 to 26.4	0.234
Length of hospital stay; d	14.5 (10.8)	12.3 (7.9)	-5.2 to 1.3	0.229
Major adverse events	9 (14.1%)	6 (8.2%)		0.274
Mortality	1 (1.6%)	1 (1.4%)		1.000

MV, mechanical ventilation; ICU, intensive care unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 10. Difference in postoperative outcomes between Risk Adjustment for Congenital Heart Surgery (RACHS) scores. Values are number (proportion) or mean (SD).

	RACHS score 1 or 2	RACHS score 3, 4 or 5	95% CI of differences	p value
Number of patients	142 (72.8%)	53 (27.2%)		
MV duration; h	44.2 (53.7)	86.5 (108.6)	-65.3 to -19.2	0.000
Length of ICU stay; h	73.1 (73.7)	199.2 (274.9)	-175.6 to -76.5	0.000
Length of hospital stay; d	10.3 (6.7)	20.7 (15.4)	-13.4 to -7.2	0.000
Major adverse events	7 (4.9%)	8 (15.1%)		0.030
Mortality	0 (0.0%)	2 (3.8%)		0.073

RACHS, Risk Adjustment for Congenital Heart Surgery; MV, mechanical ventilation; ICU, intensive care unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 11. Difference in postoperative acute kidney injury incidence between the hydroxyethyl starch (HES) and control groups according to Risk Adjustment for Congenital Heart Surgery (RACHS) score. Values are median (IQR [range]), mean (SD) or number (proportion).

	HES group n=98	Control group n=97	95% CI of differences	p value
RACHS score				
Score 1 or 2				
AKIN classification	69 (70.4%)	73 (75.3%)		0.431
AKI (-)	52 (53.1%)	59 (60.8%)		
AKI (+)	17 (17.3%)	14 (14.4%)		
pRIFLE classification	69 (70.4%)	73 (75.3%)		0.030
AKI (-)	37 (37.8%)	52 (53.6%)		
AKI (+)	32 (32.7%)	21 (21.6%)		
Score 3 or 4 or 5				
AKIN classification	29 (29.6%)	24 (24.7%)		1.000
AKI (-)	23 (23.5%)	20 (20.6%)		
AKI (+)	6 (6.1%)	4 (4.1%)		
pRIFLE classification	29 (29.6%)	24 (24.7%)		0.441
AKI (-)	21 (21.4%)	15 (15.5%)		
AKI (+)	8 (8.2%)	9 (9.3%)		

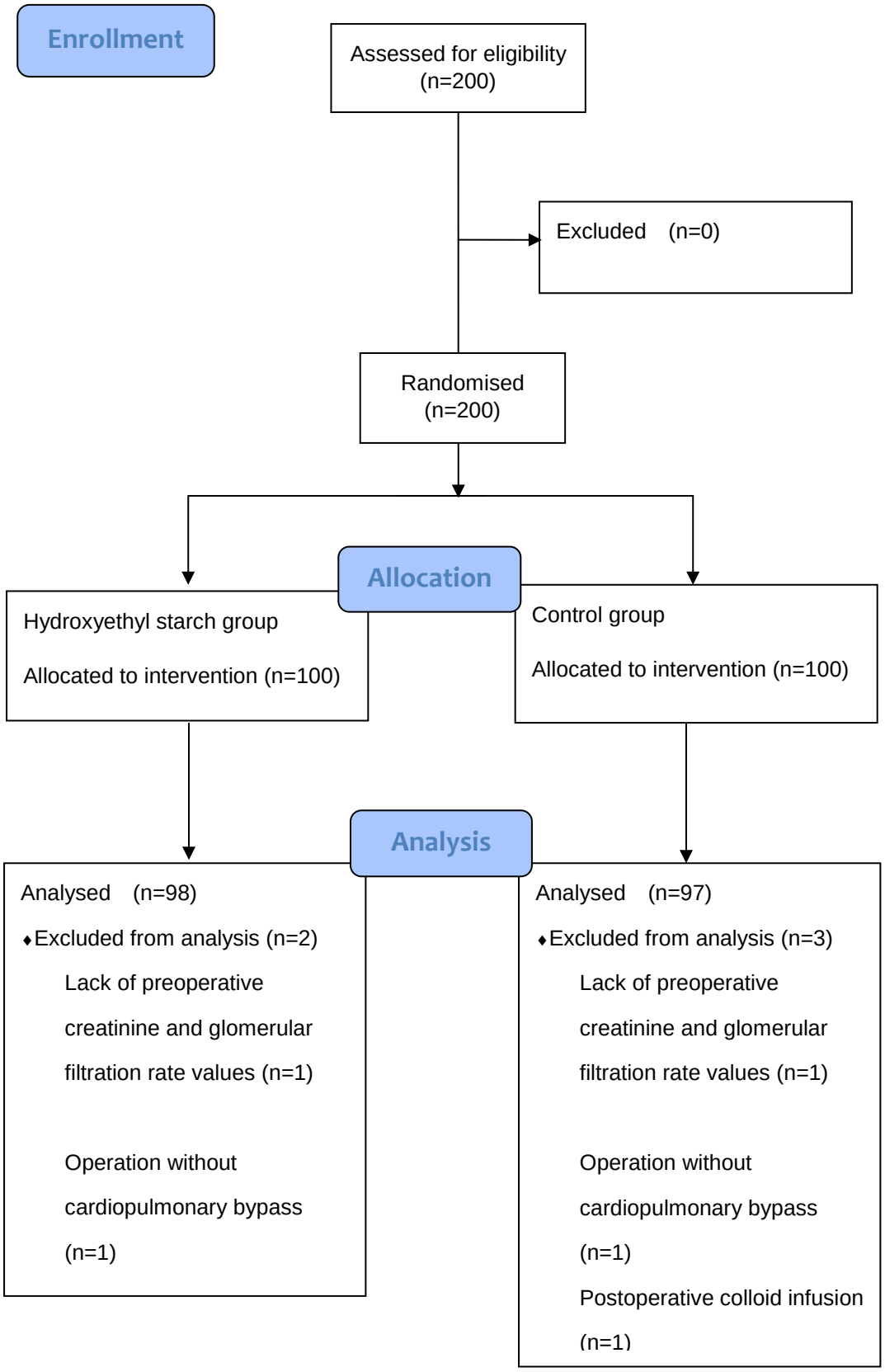
RACHS, Risk Adjustment for Congenital Heart Surgery; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Table 12. Difference in postoperative outcomes between the hydroxyethyl starch (HES) and control groups in Risk Adjustment for Congenital Heart Surgery (RACHS) score 1 or 2. Values are number (proportion) or mean (SD).

	HES group n=69	Control group n=73	95% CI of differences	p value
RACHS score 1 or 2				
MV duration; h	53.5 (68.7)	35.5 (32.0)	-35.7 to -0.4	0.045
Length of ICU stay; h	81.4 (88.3)	65.3 (56.0)	-40.4 to 8.3	0.195
Length of hospital stay; d	11.0 (6.7)	9.8 (6.7)	-3.4 to 1.0	0.284
Major adverse events	5 (7.2%)	2 (2.7%)		0.265
Mortality	0 (0.0%)	0 (0.0%)		

RACHS, Risk Adjustment for Congenital Heart Surgery; MV, mechanical ventilation; ICU, intensive care unit; AKI, acute kidney injury; pRIFLE: Paediatric Risk, Injury, Failure, Loss, End stage renal disease; AKIN: Acute Kidney Injury Network.

Figure 1. Consolidated Standards Of Reporting Trials (CONSORT) flow diagram for patients included in the study.



DISCUSSION

We found that intra-operative administration of 6% HES 130/0.4 in a volume of up to 30 $ml.kg^{-1}$ did not increase the incidence of postoperative AKI in children following cardiac surgery employing CPB and that intra-operative and postoperative transfusions were the same for both groups. Acute kidney injury in children is common following cardiac surgery, with a reported incidence of between 27% and 50% [8, 9, 20]. One major factor inducing kidney injury during cardiac surgery is CPB-related renal ischaemia. During CPB, renal vasoconstriction combined with haemodilution decreases oxygen delivery to the kidneys; further impairment occurs due to increased renal oxygen consumption, as well as possible embolisation after weaning from CPB [21, 22]. Haemodilution during CPB can result in decreased oncotic pressure and interstitial oedema; this is compounded when large fluid volumes are administered in order to maintain intravascular volume. The purpose of colloid administration is to maintain osmotic pressure and avoid interstitial fluid retention [21]. Rex et al. studied adults undergoing mitral valve replacement and found that 4% albumin added to the pump prime volume significantly increased total blood volume and reduced extravascular fluid compared with Ringer's lactate [23]. However, there are concerns regarding renal function following colloid administration. Two large randomised trials revealed negative effects of colloid administration in adult intensive care patients; 6% HES 130/0.4 (Voluven ®, Fresenius Kabi, Bad Homburg, Germany) in a volume of up to 50 $ml.kg^{-1}.day^{-1}$ and 130/0.42 (Tetraspan®, B Braun Melsungen, Melsungen, Germany) in a volume of up to 33 $ml.kg^{-1}.day^{-1}$ increased the likelihood of renal replacement therapy with relative risks of 1.21 and 1.35 respectively when compared with patients receiving crystalloids [2,3]. However these studies only included critically ill adults.

With regard to cardiac surgical patients, the safety of colloid infusions has been questioned. In a retrospective study, adults who received 6% HES 130/0.4 were twice as likely to develop postoperative AKI and a reduced urine output compared with those given crystalloids [24]. However, in one prospective multicentre cohort

study, peri-operative use of 6% HES 130/0.4 for cardiac surgery did not increase the renal replacement therapy risk (OR, 0.99) [25]. Rather, the non-HES group required more intra-operative vasopressors and had longer CPB times [25].

Few studies have assessed colloid solution efficacy and safety in children. Sumpelmann et al. evaluated 6% HES 130/0.42 in major paediatric surgery [26]. The mean (SD) infused HES volume was 10.6 (5.8) $ml.kg^{-1}$ and no serious complications, such as renal failure, were observed [26]. In neonates, volume expansion with 6% HES 200/0.5 up to 10 $ml.kg^{-1}$ did not increase serum creatinine levels [27]. Hanart et al. compared albumin with 6% HES 130/0.4 in paediatric cardiac surgical patients; the effects on renal function were comparable and there was a reduction in allogeneic transfusion [28]. However, no previous study has compared 6% HES 130/0.4 with crystalloid in terms of renal function in large numbers of paediatric patients undergoing cardiac surgery.

Several factors should be considered when interpreting our results. Firstly, the infusion volume was limited to 30 $ml.kg^{-1}$; the mean infusion volume was approximately 14 $ml.kg^{-1}$ (range 2.0–29.9 $ml.kg^{-1}$) and some patients only received small volumes of HES. Secondly, we used 6% HES 130/0.4 in a balanced solution and this has only recently been introduced clinically. Different molecular weights and degrees of substitution within HES products can elicit different effects on renal function. For example, one animal study demonstrated that 10% HES 200/0.5 induced more renal tubular damage than 6% HES 130/0.42 [29]. Finally, we excluded patients with pre-operative renal dysfunction. Our conclusions, that the effects of HES on renal function are similar to those of crystalloid should be interpreted in the context of our specific study protocol. For renal function assessment, we used pRIFLE and AKIN criteria; both have a good correlation with AKI clinical outcomes [30], but sensitivities in identifying AKI may differ between the two because the eGFR is used for pRIFLE whereas serum creatinine is used for AKIN. An AKI diagnosis based on serum creatinine may be missed because it can alter depending on volume status and eGFR calculations may increase and hence reduce the incidence of apparent AKI incidence [30]. In a previous study, the pRIFLE classification was more sensitive

at detecting AKI (51.1%) than that of AKIN (37.3%) [31] and our results reflect this; patients with AKI assessed using pRIFLE showed worse clinical outcomes after cardiac surgery than those without, as has previously been demonstrated [8, 32]. Intra-operative urine output was significantly greater in the control group than in the HES group, although urine output during CPB itself did not differ significantly between the groups. Song et al. reported that urine output during CPB could predict AKI after cardiac surgery [33] and a urine output during CPB < 1.5 $ml.kg^{-1}.h^{-1}$ was associated with AKI [34]. However, inflammation-triggered tubular damage during CPB can increase urine output [35] and our patients had relatively high urine outputs during surgery. A comprehensive approach is required for urine output interpretation during cardiac surgery.

Fluid overload results in worse postoperative outcomes [36]. A previous report by Hazle et al. demonstrated that early fluid overload or weight gain following cardiac surgery was associated with AKI in infants [37]. A study by Van der Linden et al. concluded that 6% HES 130/0.4 was associated with less positive fluid balance, without increasing the risk of renal dysfunction, compared with human albumin solution [38]. In the present study, total intra-operative fluid volume did not differ between the two groups and also we measured immediate postoperative weight and found no significant difference between children who received HES and those that received crystalloid only.

Coagulation abnormality is a possible adverse effect of colloid administration. Hydroxyethyl starch 200/0.62 is known to reduce levels of von Willebrand factor [39]. Colloids inhibit blood coagulation more than crystalloids even after allowing for haemodilution [40], and any dilutional coagulopathy is thought to be caused by acquired fibrinogen deficiency or dysfunction [41]. Another study demonstrated that 30% *in vivo* dilution with HES 130/0.4 reduced the MCF of thromboelastometry and activities of coagulation factors including factors II, VII, VIII, IX, X and XIII in adults [42]. In our study, EXTEM clotting times were longer and the FIBTEM A10 and MCF were reduced in the HES group compared with the control group. These results are similar to those of a previous report in adult patients having cardiac surgery under

CPB, but the differences between the groups were less in our study; patients who received HES (130/0.4) peri-operatively had lower FIBTEM MCF values (median, 7 mm vs. 13 mm) and significantly prolonged clot firmness durations (median, 185 s vs. 107 s) immediately postoperatively compared with those who received Ringer's lactate [43]. However, we found no significant differences in bleeding or transfusion requirements between our two groups. Two randomised controlled trials in which dextrans were compared with crystalloids found no differences in bleeding [44, 45]. Additionally, the use of 6% HES 130/0.4 as a pump prime volume of 20 $ml.kg^{-1}$ or 30 $ml.kg^{-1}$ per day did not increase peri-operative blood loss in adults undergoing cardiac surgery [46, 47]. We believe that although the ROTEM coagulation profiles in the HES group were more abnormal than in the control group, many patients did not meet transfusion criteria and therefore transfusion volumes did not differ between the groups.

In a previous retrospective study, age of less than 12 months was an independent predictor of AKI after cardiac surgery [12]. In the same context, subgroup analysis was done to evaluate the AKI incidence and postoperative outcome after cardiac surgery in young age. Although AKIN classification did not show any significant difference between the HES group and the control group, children under age 1 had higher AKI incidence in the HES group when classified with pRIFLE criteria. However postoperative outcomes were not different between two groups in patients under age 1. Further evaluation will be needed in population of this age considering immature renal tubule and its vulnerability to post-CPB inflammation and reperfusion ischemic injury.

Also Pedersen et al. identified high RACHS score as an independent risk factor for AKI in pediatric cardiac surgery as well as young age and the use of CPB [11]. Comparing this fact with our results is quite complicated because of the relative absence of patients with high category in our study. And so in higher RACHS score (score 3, 4 or 5) the incidence of AKI did not show a significant difference between the groups, patients in the HES group had significantly higher incidence of AKI in low RACHS score (score 1 or 2). It was very obvious that

postoperative outcome was worse in patients with higher RACHS score than those with lower. But the mechanical duration was longer in the HES group than the control group, compared only in the patients with RACHS score 1 or 2.

Our study has limitations. Firstly, infused HES volumes varied between patients because we set an upper limit of 30 $ml.kg^{-1}$. Secondly, we could not use urine output criteria for AKI classification based on pRIFLE because urine output measurement intervals were not constant. Thirdly, subgroup analysis could not be performed in patients with disease vulnerable to AKI, such as coarctation of aorta, because of small number of patients. Finally, we did not perform ROTEM pre-operatively and therefore could not assess any changes from baseline.

In conclusion, the intra-operative use of 6% HES 130/0.4 in paediatric cardiac surgery did not increase AKI compared with crystalloid only. The incidence of AKI was 40% and 21% according to pRIFLE and AKIN classifications, respectively, although patients with AKI showed worse clinical outcomes. Although the HES group had greater coagulopathy according to ROTEM measurements, blood loss and transfusion volumes did not differ from the control group and we believe that 6% HES 130/0.4 in a volume of up to 30 ml kg^{-1} is non-inferior to crystalloid as safely being used for volume expansion in children undergoing cardiac surgery.

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국문 초록

서론: 신장 손상은 심장 수술을 받는 어린이에게서 흔하게 나타나며 주술기 치명률과 연관이 있다. 심폐우회를 통해 심장 수술을 받는 어린이를 대상으로 수술 중 교질액 혹은 정질액을 사용하였을 때, 수술 후 신장 손상을 포함하여 예후에 미치는 영향에 대한 연구는 아직 부족하다. 본 연구진은 소아 심장 수술에서의 교질액 사용이 급성 신손상에 미치는 영향을 평가하고자 하였다.

방법: 이 연구는 2015 년 11 월부터 2016 년 11 월까지 심폐우회를 통해 정규 심장수술을 받는 7 세 미만의 소아 환자 195 명을 대상으로 하였다. 환자들은 무작위로 Hydroxyethyl starch (HES)군과 대조군으로 나뉘었다. HES 군에서는 6% HES 130/0.4 (Volulyte®)를 마취 유도, 마취 유지, 심폐우회술, 마취 종료시까지 수액보충의 우선 수액으로 사용하였고 용량을 최대 30 $ml.kg^{-1}$로 제한하였으며, 그 이상 수액이 필요할 시에는 정질액으로 대체하였다. 대조군에서는 오로지 정질액만 사용하였다. 주요 평가 항목으로 급성 신손상의 발생률, 수술 중 수혈량, 임상적 예후 및 검사수치를 비교하고자 하였다.

결과: 급성 신손상의 발생률은 Paediatric Risk, Injury, Failure, Loss, End-stage renal disease (pRIFLE)와 Acute Kidney Injury Network (AKIN) 분류법 두 가지 방법으로 평가하였고, 두 군간에 발생률 차이는 보이지 않았다 (HES 군 40.8% vs. 대조군 30.0%; p = 0.150 pRIFLE 로 평가 시; 19.6% vs. 21.1%, P = 0.602 AKIN 으로 평가 시). 또한 사망률, 중대한 이상반응, 중환자실 재원기간 및 기계환기 적용기간 등과 같은 임상적인 예후에 있어서도 두 군간의 차이는 없었다. 흉골 봉합 시 측정한 external TEMogram 의 clotting time 은 대조군보다 HES 군에서 늘어나 있었고, fibrinogen TEMogram 의 clot firmness after 10 min 와 maximal clot firmness 값은 줄어들어 있었다. 그러나 두 군간의 수혈 요구량에는 큰 차이가 없었다. 한편 급성 신손상이 발생한 환자들은 발생하지 않은 환자들에 비해 보다 나쁜 예후를 보였다.

결론: 소아 심장 수술 환자들에게서 수술 중 최대 30 $ml.kg^{-1}$의 6% HES 130/0.4 의 사용은 급성 신손상의 발생에 있어 정질액에 비해 열등하지 않다고 결론 내릴 수 있다.

주요어: 선천성 심장질환; 정질액 대 교질액; 소아; 신손상; 심폐우회술; 수술

학번: 2015-30595