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Authors

Tobey, Rajika
Cheng, Hao
Gao, Mei
et al.

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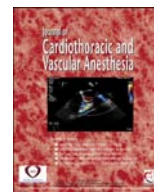10.1053/j.jvca.2016.12.024

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Postoperative Acute Kidney Injury and Blood Product Transfusion After Synthetic Colloid Use During Cardiac Surgery

Rajika Tobey, MD[*], Hao Cheng, MD[*,†], Mei Gao, MD[*,‡],
Zhongmin Li, PhD[§], J. Nilas Young, MD[‖], W. Douglas Boyd, MD[‖],
Fuhai Ji, MD[†], Hong Liu, MD[*,1]

[*]Department of Anesthesiology and Pain Medicine, University of California Davis Health System, Sacramento, CA
[†]Department of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou Shi, Jiangsu Sheng, China
[‡]Department of Anesthesiology, First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
[§]Department of Internal Medicine University of California Davis Health System, Sacramento, CA
[‖]Department of Surgery, University of California Davis Health System, Sacramento, CA

Objectives: This study assessed the effect of 2 types of hydroxyethyl starches (HES) on renal integrity and blood transfusion in cardiac surgery patients.
Design: Retrospective investigation.
Setting: Patients from a single tertiary medical center.
Participants: Inclusion criteria included coronary artery bypass graft (CABG) and/or valve surgery that included cardiopulmonary bypass with aortic cross-clamping.
Interventions: Intraoperative HES and blood product administration.
Measurements and Main Results: The study comprised 1,265 patients who met inclusion criteria. Of these patients, 70% received HES, and of these, 47% received $< 1,000$ mL and 53% received $\geq 1,000$ mL. There was no difference in the development of acute kidney injury between the 2 groups. A parsimonious propensity model for colloids showed that combined CABG and valve surgery were less likely to be associated with HES administration than was CABG alone (OR 0.68, confidence interval [CI] 0.46-0.97; p = 0.04). Intra-aortic balloon pump use was less likely to be associated with HES administration (OR 0.57, CI 0.38-0.86; p = 0.007). Patients with chronic kidney disease, stages 3 to 5, were less likely to receive HES, with an OR of 0.56 (CI 0.38-0.84; p = 0.004); 0.51 (CI 0.20-1.33; p = 0.170); and 0.23 (CI 0.12-0.44; p < 0.0001), respectively, for each stage. No difference was noted in red blood cell transfusion. However, fresh frozen plasma, cryoprecipitate, and platelet transfusions were significantly higher with larger volumes of HES, with an OR of 2.03 (CI 1.64-2.52; p < 0.001); 1.60 (CI 1.30-1.97; p < 0.000); and 1.62 (CI 1.21-2.15; p = 0.006), respectively. No differences in surgical mortality were found between the colloid and noncolloid groups.
Conclusions: This study showed no association of postoperative acute kidney injury and red blood cell transfusion between the colloid and noncolloid groups. Although the complication rate was higher with HES administration, there was no difference in surgery mortality between the 2 groups.
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Key Words: synthetic colloid; hydroxyethyl starch; acute kidney injury; cardiopulmonary bypass; blood products

SINCE THEIR INTRODUCTION in the 1960s, hydroxyethyl starches (HES) continue to be used as volume expanders in conjunction with crystalloids.[1] Due to some studies highlighting increased acute kidney injury (AKI) and overall adverse effects with HES in the critically ill population, the choice of fluids in patients experiencing sepsis has become important.[2-4] The safety of HES in the perioperative setting, specifically in cardiovascular surgery, remains unclear due to a

few small, single-outcome studies and conflicting results.[5-8] Cardiopulmonary bypass (CPB) surgery, in particular, is prone to large fluid shifts necessitating aggressive fluid resuscitation. Colloids such as HES have become an efficient and affordable adjunct to crystalloids in maintaining intravascular volume and tissue perfusion.

Incidence of AKI after coronary artery bypass graft (CABG) surgery can be as high as 54%, depending on the definition of AKI, and is associated with 60% mortality, which inevitably leads to higher healthcare costs.[9-12] CPB also interferes with coagulation due to platelet dysfunction, a decrease in coagulation factors, and an increase in fibrinolytic activity[13]; therefore, the colloid choice used to maintain intravascular volume must not compound the bleeding risk that pre-exists in cardiac surgery.

HES is derived from potato starch or waxy maize. To suit the evolving understanding of these products' pharmacodynamics and pharmacokinetics, manufacturers have changed HES production from pentastarches with higher mean molecular weight (≥ 200 kD), molar substitution, and hydroxyethylation ratios to newer-generation tetrastarches with lower mean molecular weight (130 kD), molar substitution, and hydroxyethylation ratios.[14] A higher molar substitution and hydroxyethylation ratio are believed to be linked with slow degradation,[15] which then may result in accumulation of HES in plasma, interstitial space, reticuloendothelial system, and epithelial cells, leading to impaired coagulation, nephrotoxicity, and pruritus.[16,17] Clinical studies have shown a significantly higher concentration of HES 200/0.5 remaining in plasma compared with HES 130/0.4 after 24 hours.[18]

Studies comparing HES products during cardiac surgery have yielded conflicting results. The lack of data quality has occurred due to small cohorts, predominantly single HES type (eg, 130/0.4), and assessment of single primary endpoints, such as either renal failure or bleeding. At least 3 meta-analyses on the effect of HES on the surgical population have been published in the last 4 years,[5,6,19] but 2 concentrated only on kidney function,[5,19] and all included heterogenous groups such as cardiac, abdominal, or orthopedic. To further complicate the results, several surgical studies, including cardiac surgery, were retracted after scientific misconduct.[20] Recently, there have been a few new observational studies on HES and AKI in noncardiac surgeries.[7,8] The aim of this study was to examine specifically the cardiac surgical population due to the unique physiologic changes to which CPB predisposes patients and to compare 2 different types of 6% HES and their effects on the development of postoperative AKI and the need for blood product transfusion compared with patients who did not receive HES.

Methods

Study Design

With permission from the University of California Davis Institutional Review Board, patients who underwent cardiac surgery were identified from the institutional Society of Thoracic Surgeons (STS) database, and medical records from July 1, 2007 to June 30, 2013 were located. Inclusion criteria included adult patients who underwent CPB with aortic cross-clamping, CABG, valve, or combination surgery. Exclusion criteria included patients who did not undergo CPB, the pediatric population, emergency surgery, deep hypothermic circulatory arrest, and surgeries that did not involve the coronary artery or valve. Study participants were divided into the 2 following groups: colloid group (n = 887) and noncolloid group (n = 378) depending on intraoperative HES administration. The HES used at the authors' institution included Voluven (6% HES 130/0.4; Pfizer, New York, NY) and Hextend (6% HES 670/0.75; BioTime, Alameda, CA).

Data Collection

Patient demographics, history, preoperative risk factors, preoperative medications, intraoperative data, baseline and postoperative kidney function, blood administration, bypass and cross-clamp time, all complications, and surgical mortality were obtained from the STS database (Table 1). Patient anesthesia records were reviewed through electronic medical records and paper charts for intraoperative HES documentation.

Primary and Secondary Outcomes

Postoperative AKI and blood product transfusions were the primary outcomes of this study. Secondary outcomes included postoperative complications and surgical mortality. Baseline kidney function was based on the preoperative estimated glomerular filtration rate (eGFR [mL/min/1.73m^2]) that was calculated using the Modification of Diet in Renal Disease equation.[21] Patients were divided into the following 5 stages: stage 1, normal eGFR (> 90); stage 2, mildly decreased eGFR (60-89); stage 3, moderately decreased eGFR (30-59); stage 4, severely decreased eGFR (15-29); and stage 5, kidney failure or dialysis (eGFR < 15). The STS definition of postoperative renal failure was used to determine postoperative AKI. This definition included the highest creatinine (Cr) level recorded in the postoperative course that was ≥ 3-fold times the baseline Cr or Cr ≥ 4, with an acute increase of ≥ 0.5 mg/dL or new requirement for dialysis.

Blood product transfusion was based on intraoperative and postoperative administration of packed red blood cells (PRBCs), fresh frozen plasma (FFP), cryoprecipitate (cryo), and platelets.

Surgical mortality was defined by the STS as death during hospital admission or within 30 days of discharge. All complications are an STS umbrella term that includes any complication that occurred postoperatively, such as pulmonary, infectious, renal, cardiac, or vascular complications or redo surgery.

Statistical Analysis

Continuous variables were reported as mean $\pm$ standard deviation or percentages and were compared with the *t*-tests or chi-square test (2-tailed), respectively. Univariate and

Table 1
Baseline Patient Characteristics

Variables		Total, n (%)	No Colloids Used	Colloids Used, n (%)	p Value
		n = 1,265 (100.0%)	n = 378 (29.9%)	n = 887 (70.1%)	
Age, yr, mean (SD)			61.7 (13.4)*	62.3 (12.3)*	0.404
Sex	Female	376 (29.7)	127 (33.6)	249 (28.1)	0.049
	Male	889 (70.3)	251 (66.4)	638 (71.9)	
Race	White	830 (65.6)	223 (59)	607 (68.4)	0.001
	Other	435 (34.4)	155 (41)	280 (31.6)	
Surgery status	Elective	587 (46.4)	168 (44.4)	419 (47.2)	0.571
	Urgent	678 (53.6)	210 (55.6)	468 (52.8)	
Surgery type	CABG only	591 (46.7)	161 (42.6)	430 (48.5)	0.138
	CABG+other	68 (5.4)	17 (4.5)	51 (5.7)	
	CABG+valve	175 (13.8)	63 (16.7)	112 (12.6)	
	CABG+valve+other	69 (5.5)	21 (5.6)	48 (5.4)	
	Valve	220 (17.4)	65 (17.2)	155 (17.5)	
	Valve+other	142 (11.2)	51 (13.5)	91 (10.3)	
CKD stage	1: < 90	315 (24.9)	80 (21.2)	235 (26.5)	< 0.0001
	2: 60-89	642 (50.8)	176 (46.6)	466 (52.5)	
	3: 30-59	236 (18.7)	83 (22)	153 (17.2)	
	4: 15-29	20 (1.6)	8 (2.1)	12 (1.4)	
	5: < 15 or dialysis	52 (4.1)	31 (8.2)	21 (2.4)	
BMI	< 18.5	11 (0.9)	7 (1.9)	4 (0.5)	0.048
	18.5-39.9	1,165 (92.1)	344 (91)	821 (92.6)	
	≥ 40	89 (7)	27 (7.1)	62 (7.0)	
Diabetes	No	797 (63)	241 (63.8)	556 (62.7)	0.717
	Yes	468 (37)	137 (36.2)	331 (37.3)	
Hypertension	No	318 (25.1)	101 (26.7)	217 (24.5)	0.397
	Yes	947 (74.9)	277 (73.3)	670 (75.5)	
Hypocholesteremia	No	310 (24.5)	109 (28.8)	201 (22.7)	0.019
	Yes	955 (75.5)	269 (71.2)	686 (77.3)	
Smoking	No	687 (54.3)	195 (51.6)	492 (55.5)	0.205
	Yes	578 (45.7)	183 (48.4)	395 (44.5)	
CVA	No	1,154 (91.2)	345 (91.3)	809 (91.2)	0.971
	Yes	111 (8.8)	33 (8.7)	78 (8.8)	
Cardiogenic shock	No	1,253 (99.1)	375 (99.2)	878 (99)	0.711
	Yes	12 (0.9)	3 (0.8)	9 (1.0)	
Previous MI	No	818 (64.7)	246 (65.1)	572 (64.5)	0.840
	Yes	447 (35.3)	132 (34.9)	315 (35.5)	
CHF	No	755 (59.7)	201 (53.2)	554 (62.5)	0.002
	Yes	510 (40.3)	177 (46.8)	333 (37.5)	
IABP	No	1,146 (90.6)	330 (87.3)	816 (92.0)	0.009
	Yes	119 (9.4)	48 (12.7)	71 (8.0)	
Cerebrovascular disease	No	1,047 (82.8)	311 (82.3)	736 (83.0)	0.762
	Yes	218 (17.2)	67 (17.7)	151 (17.0)	
Previous CV intervention	No	971 (76.8)	282 (74.6)	689 (77.7)	0.236
	Yes	294 (23.2)	96 (25.4)	198 (22.3)	
Previous CABG	No	1,217 (96.2)	362 (95.8)	855 (96.4)	0.594
	Yes	48 (3.8)	16 (4.2)	32 (3.6)	
Previous valve surgery	No	1,209 (95.6)	358 (94.7)	851 (95.9)	0.329
	Yes	56 (4.4)	20 (5.3)	36 (4.1)	
Other cardiac intervention	No	1,234 (97.5)	366 (96.8)	868 (97.9)	0.277
	Yes	31 (2.5)	12 (3.2)	19 (2.1)	
Dialysis	No	1,218 (96.3)	349 (92.3)	869 (98)	< 0.0001
	Yes	47 (3.7)	29 (7.7)	18 (2)	
Left main coronary artery disease	No	990 (78.3)	302 (79.9)	688 (77.6)	0.358
	Yes	275 (21.7)	76 (20.1)	199 (22.4)	
Preoperative beta-blocker	No	432 (34.2)	118 (31.2)	314 (35.4)	0.151
	Yes	833 (65.8)	260 (68.8)	573 (64.6)	
Preoperative ACEi/ARB	No	668 (52.8)	187 (49.5)	481 (54.2)	0.121
	Yes	597 (47.2)	191 (50.5)	406 (45.8)	
Preoperative nitrates	No	1,218 (96.3)	363 (96)	855 (96.4)	0.756
	Yes	47 (3.7)	15 (4)	32 (3.6)	

Table 1 (*continued*)

Variables		Total, n (%)	No Colloids Used	Colloids Used, n (%)	p Value
		n = 1,265 (100.0%)	n = 378 (29.9%)	n = 887 (70.1%)	
Preoperative anticoagulants	No	1,000 (79.1)	301 (79.6)	699 (78.8)	0.742
	Yes	265 (20.9)	77 (20.4)	188 (21.2)	
Preoperative warfarin use	No	1,165 (92.1)	343 (90.7)	822 (92.7)	0.244
	Yes	100 (7.9)	35 (9.3)	65 (7.3)	
Preoperative steroids	No	1,226 (96.9)	364 (96.3)	862 (97.2)	0.404
	Yes	39 (3.1)	14 (3.7)	25 (2.8)	
Preoperative aspirin	No	350 (27.7)	111 (29.4)	239 (26.9)	0.378
	Yes	915 (72.3)	267 (70.6)	648 (73.1)	
Preoperative lipid-lowering medications	No	321 (25.4)	111 (29.4)	210 (23.7)	0.033
	Yes	944 (74.6)	267 (70.6)	677 (76.3)	
Preoperative GPIIbIIIa inhibitor	No	1,221 (96.5)	368 (97.4)	853 (96.2)	0.291
	Yes	44 (3.5)	10 (2.6)	34 (3.8)	
Last creatinine level (mg/dL)			1.53 (1.66)[*]	1.14 (0.80)[*]	< 0.0001
EF (%)			50.8 (13.8)[*]	52.6 (13.1)[*]	0.029
Cross-clamp time			133.2 (57.2)	126.7 (55.7)	0.059
Perfusion time			189.5 (76.9)	178.7 (69.3)	0.019
Propensity score			0.666 (0.117)[*]	0.714 (0.091)[*]	< 0.0001

Abbreviations: ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; CEi, angiotensin converting enzyme inhibitor; CKD, chronic kidney diseases; CHF, congestive heart failure; CV, cardiovascular; CVA, cerebral vascular accident; EF, ejection fraction; GPIIbIIIa, glycopritein IIb/IIIa; IABP, intra-aortic balloon pump; MI, myocardial infarction; SD, standard deviation.

[*]Statistically significant.

multivariate logistic regressions were performed to assess associations of demographic, therapeutic, and clinical outcome variables. To mitigate selection bias in HES administration, the propensity score was computed, with the conditional probability of each patient receiving HES with a multivariable logistic regression model that included patient risk factors (see Table 1).

To achieve model parsimony and stability, the backward selection procedure was applied with the dropout criterion p > 0.05. The candidate risk factors were selected according to clinical plausibility and variables collected in the database. The candidate independent variables included demographic and clinical risk factors (see Table 1). The parsimonious multivariable propensity for HES use included status of procedure, type of surgery, and level of pre-existing chronic kidney disease (CKD) (Fig 1). The risk-adjusted odds ratios (OR) for all outcomes were calculated with use of a stepwise logistic-regression model, with patient risk factors as independent control variables and HES use as the independent variable of interest. A propensity-weighted logistic regression model

Effect		Odds Ratio	95% Confidence Limits		p value	OR (95% CI)
Age	For every additional year	1.002	0.991	1.014	0.660	
Sex	Male v female	1.210	0.914	1.602	0.184	
Race	Non-Caucasian v Caucasian	0.743	0.567	0.974	0.031	
Surgical type	CABG + Other v CABG	1.220	0.668	2.227	0.518	
	CABG + Valve v CABG	0.677	0.464	0.986	0.042	
	CABG + Valve + Other v CABG	0.905	0.512	1.599	0.731	
	Valve v CABG	0.980	0.654	1.470	0.924	
	Valve + Other v CABG	0.746	0.475	1.173	0.204	
Procedure status	Urgent/emergent v 1: elective	0.950	0.721	1.252	0.717	
CKD stage	Stage 2: 60-89 v stage 1: >90	0.820	0.592	1.136	0.233	
	Stage 3: 30-59 v stage 1: >90	0.563	0.379	0.836	0.004	
	Stage 4: 15-29 v stage 1: >90	0.513	0.198	1.330	0.170	
	Stage 5 v stage 1: >90	0.229	0.121	0.435	< 0.0001	
Hypercholesterolemia	Yes v no	1.409	1.012	1.961	0.042	
IABP	Yes v no	0.566	0.375	0.855	0.007	

C = 0.632

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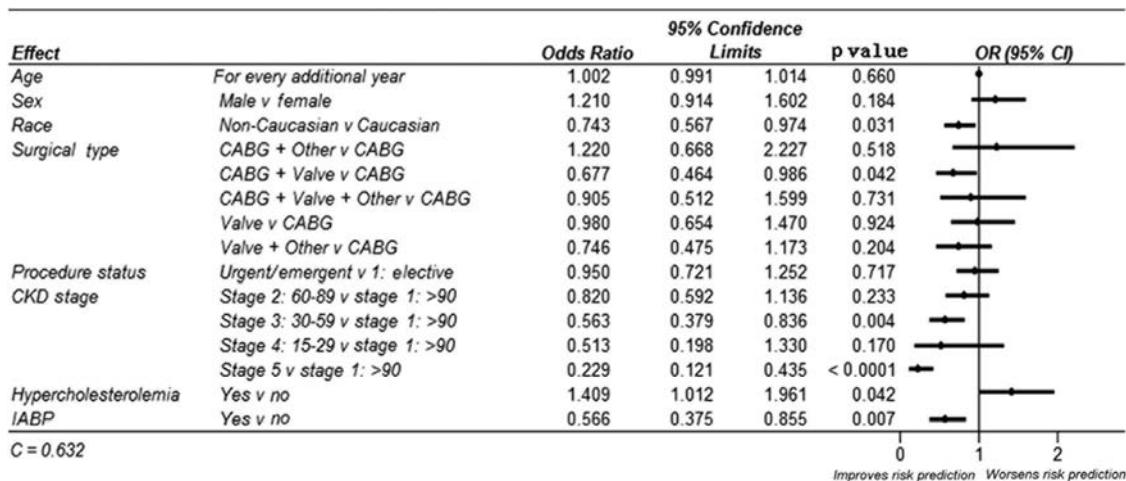*Improves risk prediction   Worsens risk prediction*

Fig 1. The parsimonious propensity model for colloids. The following risk factors were entered in the model development as candidate variables for predicting colloid use: age, sex, race, category of surgeries, emergency status, CKD stages, BMI, hypercholesterolemia, smoking, cerebral vascular accident, cerebrovascular diseases, cardiogenic shock, circulatory arrest, previous cardiovascular interventions, previous CABG, previous valve surgeries, other cardiac interventions, dialysis, last creatinine level, previous myocardial infarction, congestive heart failure, IABP, ejection fraction, left main coronary artery disease, preoperative lipid-lowering medications, cross-clamp time, and perfusion time. The parsimony was achieved by backward selection at alpha = 0.05 except the first 6 variables, which were forced into the final parsimonious model.

Table 2
Observed Outcomes of Colloids Versus No Colloids

		n (%)	AKI n (%)	p Value	Complications (Any) n (%)	p Value	Surgical Death n (%)	P Value	MACE n (%)	p Value	Total RBC ≥ 1 n (%)	p Value	Total FFP ≥ 6 n (%)	p Value	Total Cryo ≥ 2 n (%)	p Value	Total Platelets ≥ 2 n (%)	p Value
Intraoperative colloids	No	378 (29.9)	39 (10.3)	0.021*	173 (45.8)	0.795	8 (2.1)	0.473	102 (26.98)	0.989	70 (18.52)	0.765	100 (26.46)	0.536	109 (28.84)	0.415	410 (10.58)	0.911
	Yes	887 (70.1)	58 (6.5)		413 (46.6)		25 (2.8)		239 (26.94)		158 (17.81)		220 (24.80)		236 (26.61)		92 (10.37)	
Intraoperative colloids	0) No HES	378 (29.9)	39 (10.3)	0.062	173 (45.8)	0.924	8 (2.1)	0.665	102 (26.98)	0.553	70 (18.52)	0.212	100 (26.46)	0.197	109 (28.84)	0.010*	40 (10.58)	0.410
	1) < 1,000	415 (32.8)	29 (6.99)		191 (46.02)		13 (3.13)		119 (28.67)		64 (15.42)		92 (22.17)		91 (21.93)		37 (8.92)	
	2) ≥ 1,000	472 (37.3)	29 (6.14)		222 (47.03)		12 (2.54)		120 (25.42)		94 (19.92)		128 (27.12)		145 (30.72)		55 (11.65)	
Voluven	0) No Voluven	378 (42.3)	39 (10.3)	0.070	173 (45.8)	0.445	8 (2.1)	0.916	102 (26.98)	0.845	70 (18.52)	0.095	100 (26.46)	< 0.0001*	109 (28.84)	0.003*	40 (10.58)	0.028*
	1) < 1,000	208 (23.3)	16 (7.69)		84 (40.38)		5 (2.40)		58 (27.88)		26 (12.50)		21 (10.10)		44 (21.15)		11 (5.29)	
	2) ≥ 1,000	308 (34.5)	17 (5.52)		133 (43.18)		8 (2.60)		79 (25.65)		60 (19.48)		59 (19.16)		108 (35.06)		38 (12.34)	
Hextend	0) No Hextend	378 (50.47)	39 (10.32)	0.202	173 (45.8)	0.137	8 (2.1)	0.446	102 (26.98)	0.623	70 (18.52)	0.806	100 (26.46)	0.001*	109 (28.84)	0.153	40 (10.58)	0.726
	1) < 1,000	207 (27.64)	13 (6.28)		107 (51.69)		8 (3.86)		61 (29.47)		38 (18.36)		71 (34.30)		47 (22.71)		26 (12.56)	
	2) ≥ 1,000	164 (21.90)	12 (7.32)		89 (54.27)		4 (2.44)		41 (25.00)		34 (20.73)		69 (42.07)		37 (22.56)		17 (10.37)	

Abbreviation: AKI, acute kidney injury; cryo, cryoprecipitate; FFP, fresh frozen plasma; MACE, major adverse cardiocerebral events; RBC, red blood cell.
*p value < 0.05 considered statistically significant.

was used for surgical mortality in which an inverse (estimated) propensity score as weights for patients given HES and the inverse of 1 minus the propensity score for patients not given HES and added HES as an independent factor to the model. All models-fit analyses were evaluated using the Hosmer-Lemeshow goodness-of-fit statistic. The C-statistic measures predictive power. Based on the propensity of HES use and general linear model, the propensity-weighted and risk adjusted surgical mortality were compared between the HES and no HES cohorts. Results are reported as percentages and ORs, with 95% confidence intervals. All reported p values were 2-sided, and p values < 0.05 were considered to be statistically significant. Statistical analysis was performed with SAS, version 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

Baseline and Intraoperative Parameters

Of the total 1,762 patient records, 1,268 patients met inclusion criteria; however, 3 anesthesia records could not be located, which brought the final cohort to 1,265 patients. Of the study participants, 70% received HES, and 47% of those received < 1,000 mL of HES and 53% received ≥ 1,000 mL of HES. The HES group was further divided into the Voluven and Hextend subgroups to differentiate outcomes between the 2 colloids. Demographics and patient characteristics show sex, race, hypercholesterolemia, lipid-lowering agents, ejection fraction, intra-aortic balloon pump (IABP), and bypass time significantly correlating with HES use (see Table 1). Also, patients in CKD stage 3 or higher were less likely to receive HES. Cr was more likely to be lower in the colloid group. Propensity scores for the 2 groups were used in the calculation of adjusted ORs when analyzing postoperative outcomes. Zero mL of HES use was considered to be the reference point when calculating OR. The parsimonious propensity model for colloids (see Fig 1) showed that combined CABG and valve surgeries were less likely to be associated with HES administration than was CABG alone (OR 0.68, p = 0.04). Also, patients with an IABP were less likely to be given HES (OR 0.57; p = 0.007). In addition, patients with CKD stages 3 through 5 were less likely to receive HES, with an OR 0.56 (p = 0.004), 0.51 (p = 0.170), and 0.23 (p < 0.0001), respectively for the 3 stages.

Effects of HES on Postoperative AKI

Overall incidence of AKI was less in the colloid group, with 6.5% versus 10.3% in the noncolloid group (p = 0.021) (Table 2). The propensity-weighted adjusted OR showed no difference in AKI development between the colloid and noncolloid groups (Fig 2). This correlation persisted in the Hextend and Voluven groups. The data to determine whether colloids were associated with worsening of pre-existing CKD also were analyzed. Results showed no difference in the development of AKI in various CKD stages (Table 3). The parsimonious model for predicting AKI showed that age, combined CABG and valve surgeries, longer bypass times,

urgency, pre-existing CKD, diabetes, history of cerebral vascular accident, history of prior cardiac intervention, and hypercholesterolemia all were associated with AKI. Other surgeries combined with CABG, whether valve or unspecified, proved to be the biggest risk factor for predicting AKI.

Effects of HES on Blood Product Transfusion

Overall, no significant difference was noted in the use of PRBC between the colloid and noncolloid groups (see Fig 2). However, the transfusions of FFP (OR 2.03; $p < 0.0001$), cryo (OR 1.60; $p = 0.000$), and platelets (OR 1.62; $p = 0.006$) were significantly higher in the $\geq 1,000$ mL colloid group. The colloid group that received $< 1,000$ mL did not demonstrate this difference.

Effects of HES on Secondary Outcomes

No statistical differences were demonstrated in the overall incidence of surgical death between the 2 groups, both in the high- and low-volume cohorts (see Fig 2). The parsimonious model for predicting surgical mortality showed age, female sex, combined CABG and valve surgeries, urgency, diabetes, CKD stage 5, body mass index (BMI) ≥ 40, cardiogenic shock, IABP, bypass time, and prior valve surgery to be associated with increased mortality. Combined CKD 5, BMI ≥ 40, cardiogenic shock, IABP, and previous valve surgery were observed to be the highest mortality predictors.

The observed incidence of postoperative complications was 46.6% in the colloid versus 45.8% in the noncolloid group ($p = 0.795$) (see Table 2). Fig 2 shows that overall postoperative complications were higher, with an OR of 1.38, in the $< 1,000$ mL HES group ($p = 0.004$) compared with 1.46 in the $\geq 1,000$ mL HES group ($p < 0.001$). This significantly higher OR also extended to the high-volume Voluven (OR 1.33; $p = 0.035$) and high- and low-volume Hextend groups (OR 1.59; $p = 0.002$ and OR 1.63; $p = 0.002$, respectively). The parsimonious model for predicting postoperative complications showed that age, combined CABG and valve surgeries, urgency, pre-existing CKD, BMI ≥ 40, cardiogenic shock, congestive heart failure, IABP, both low- and high-volume HES all were associated with occurrence of postoperative complications. Cardiogenic shock by far was the biggest factor predicting postoperative complications.

Major adverse cardiocerebral events (MACE) often allow studies to target cardiac-specific complications. Because no specific definition of MACE exists, for this study MACE was defined as death, myocardial infarction, repeat revascularization, and postoperative stroke. The results showed a significantly increased adjusted OR of 1.36 ($p = 0.011$) in the lower-volume colloid group (see Fig 2). This result also extended to the lower-volume Voluven group, with an OR of 1.40 ($p = 0.030$). Results were not significant in the Hextend group. The parsimonious model for predicting MACE showed that other than low-volume HES, combined CABG plus valve cases, urgency, CKD 5, BMI ≥ 40, and congestive

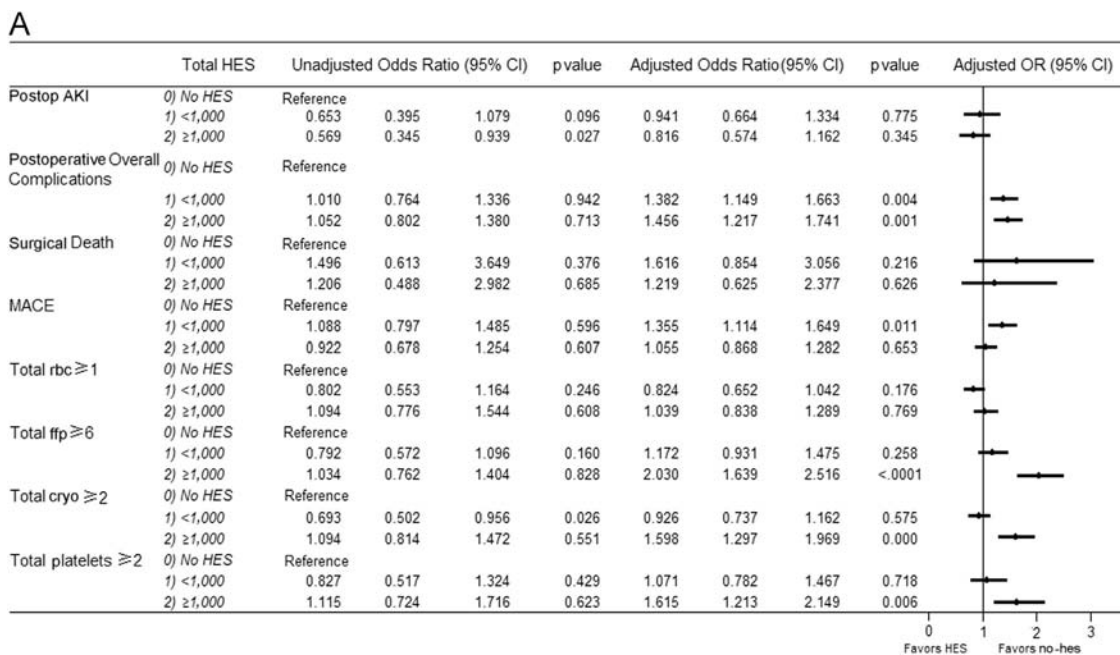| A		Total HES	Unadjusted Odds Ratio (95% CI)			p value	Adjusted Odds Ratio (95% CI)			p value	Adjusted OR (95% CI)
Postop AKI	0) No HES	Reference									
	1) <1,000	0.653	0.395	1.079		0.096	0.941	0.664	1.334	0.775	
	2) ≥1,000	0.569	0.345	0.939		0.027	0.816	0.574	1.162	0.345	
Postoperative Overall Complications	0) No HES	Reference									
	1) <1,000	1.010	0.764	1.336		0.942	1.382	1.149	1.663	0.004	
	2) ≥1,000	1.052	0.802	1.380		0.713	1.456	1.217	1.741	0.001	
Surgical Death	0) No HES	Reference									
	1) <1,000	1.496	0.613	3.649		0.376	1.616	0.854	3.056	0.216	
	2) ≥1,000	1.206	0.488	2.982		0.685	1.219	0.625	2.377	0.626	
MACE	0) No HES	Reference									
	1) <1,000	1.088	0.797	1.485		0.596	1.355	1.114	1.649	0.011	
	2) ≥1,000	0.922	0.678	1.254		0.607	1.055	0.868	1.282	0.653	
Total rbc ≥1	0) No HES	Reference									
	1) <1,000	0.802	0.553	1.164		0.246	0.824	0.652	1.042	0.176	
	2) ≥1,000	1.094	0.776	1.544		0.608	1.039	0.838	1.289	0.769	
Total ffp ≥6	0) No HES	Reference									
	1) <1,000	0.792	0.572	1.096		0.160	1.172	0.931	1.475	0.258	
	2) ≥1,000	1.034	0.762	1.404		0.828	2.030	1.639	2.516	<.0001	
Total cryo ≥2	0) No HES	Reference									
	1) <1,000	0.693	0.502	0.956		0.026	0.926	0.737	1.162	0.575	
	2) ≥1,000	1.094	0.814	1.472		0.551	1.598	1.297	1.969	0.000	
Total platelets ≥2	0) No HES	Reference									
	1) <1,000	0.827	0.517	1.324		0.429	1.071	0.782	1.467	0.718	
	2) ≥1,000	1.115	0.724	1.716		0.623	1.615	1.213	2.149	0.006	

0 1 2 3
Favors HES   Favors no-hes

Fig 2. (A) Unadjusted versus propensity-weighted and risk adjusted ORs of total colloids use on postoperative outcomes. (B) Unadjusted versus propensity-weighted and risk adjusted ORs of Voluven use on postoperative outcomes. (C) Unadjusted versus propensity-weighted and risk adjusted ORs of Hextend use on postoperative outcomes. The following risk factors were entered in the model development as candidate variables for predicting postoperative outcomes with inverse propensity weighting of intraoperative colloids use: total HES/Voluven/Hextend, age, sex, race, category of surgeries, emergency status, CKD stage, crystalloids, BMI, smoking, cerebral vascular accident, cerebrovascular disease, cardiogenic shock, circulatory arrest, previous cardiovascular intervention, previous CABG, previous valve surgeries, other cardiac intervention, dialysis, last creatinine level, previous myocardial infarction, congestive heart failure, IABP, ejection fraction, and left main coronary artery disease. The parsimony was achieved by a backward selection at alpha = 0.05 except the first 8 variables, which were forced in the final parsimonious model.

B

	Voluven	Unadjusted Odds Ratio (95% CI)			pvalue	Adjusted Odds Ratio(95% CI)			pvalue	Adjusted OR (95% CI)
Postop AKI	0) No Voluven	Reference								
	1) <1,000	0.724	0.394	1.331	0.299	1.181	0.746	1.872	0.552	
	2) ≥1,000	0.508	0.281	0.917	0.025	0.711	0.449	1.126	0.223	
Postoperative Overall Complications	0) No Voluven	Reference								
	1) <1,000	0.803	0.570	1.131	0.209	1.198	0.936	1.535	0.229	
	2) ≥1,000	0.901	0.665	1.219	0.498	1.325	1.064	1.651	0.035	
Surgical Death	0) No Voluven	Reference								
	1) <1,000	1.139	0.368	3.528	0.821	0.858	0.321	2.295	0.798	
	2) ≥1,000	1.233	0.457	3.325	0.679	0.863	0.364	2.047	0.779	
MACE	0) No Voluven	Reference								
	1) <1,000	1.033	0.733	1.456	0.853	1.401	1.085	1.810	0.030	
	2) ≥1,000	0.922	0.681	1.247	0.597	1.144	0.911	1.438	0.331	
Total RBC ≥1	0) No Voluven	Reference								
	1) <1,000	0.611	0.389	0.957	0.032	0.667	0.479	0.928	0.044	
	2) ≥1,000	1.034	0.739	1.447	0.845	1.096	0.852	1.411	0.549	
Total FFP ≥6	0) No Voluven	Reference								
	1) <1,000	0.238	0.148	0.384	<0.0001	0.357	0.244	0.521	<0.0001	
	2) ≥1,000	0.503	0.364	0.694	<0.0001	1.046	0.805	1.361	0.776	
Total cryo ≥2	0) No Voluven	Reference								
	1) <1,000	0.773	0.534	1.120	0.174	1.025	0.756	1.389	0.895	
	2) ≥1,000	1.556	1.169	2.070	0.002	2.372	1.864	3.019	<0.0001	
Total platelets ≥2	0) No Voluven	Reference								
	1) <1,000	0.448	0.234	0.857	0.015	0.622	0.374	1.035	0.125	
	2) ≥1,000	1.129	0.750	1.700	0.560	1.854	1.339	2.566	0.002	

0 1 2 3
Favors Voluven   Favors no-voluven

C

	Hextend	Unadjusted Odds Ratio (95% CI)			p-value	Adjusted Odds Ratio (95% CI)			p-value	Adjusted OR(95%CI)
Postop AKI	0) No Hextend	Reference								
	1) <1,000	0.582	0.303	1.118	0.104	0.741	0.459	1.196	0.303	
	2) ≥1,000	0.686	0.350	1.347	0.274	1.007	0.610	1.664	0.981	
Postoperative Overall Complications	0) No Hextend	Reference								
	1) <1,000	1.268	0.903	1.780	0.171	1.589	1.248	2.023	0.002	
	2) ≥1,000	1.406	0.973	2.031	0.069	1.630	1.255	2.117	0.002	
Surgical Death	0) No Hextend	Reference								
	1) <1,000	1.859	0.687	5.029	0.222	3.632	1.612	8.181	0.009	
	2) ≥1,000	1.156	0.343	3.895	0.815	1.611	0.641	4.051	0.395	
MACE	0) No Hextend	Reference								
	1) <1,000	1.145	0.820	1.598	0.426	1.213	0.948	1.551	0.197	
	2) ≥1,000	0.914	0.623	1.340	0.644	0.839	0.632	1.113	0.307	
Total RBC ≥1	0) No Hextend	Reference								
	1) <1,000	1.064	0.719	1.574	0.757	1.010	0.761	1.341	0.955	
	2) ≥1,000	1.237	0.817	1.874	0.315	0.973	0.713	1.328	0.886	
Total FFP ≥6	0) No Hextend	Reference								
	1) <1,000	2.071	1.488	2.881	<0.0001	1.977	1.522	2.568	<0.0001	
	2) ≥1,000	2.881	2.029	4.090	<0.0001	3.116	2.366	4.103	<0.0001	
Total cryo ≥2	0) No Hextend	Reference								
	1) <1,000	0.712	0.499	1.017	0.062	0.762	0.572	1.016	0.121	
	2) ≥1,000	0.707	0.477	1.047	0.084	0.736	0.536	1.011	0.113	
Total platelets ≥2	0) No Hextend	Reference								
	1) <1,000	1.299	0.816	2.070	0.270	1.315	0.925	1.869	0.201	
	2) ≥1,000	1.046	0.605	1.809	0.872	1.025	0.669	1.568	0.925	

0 1 2 4 6 8
Favors Hextend   Favors no-hextend

Fig 2. (continued)

heart failure to be positively associated with MACE. Type of case and end-stage CKD were the biggest culprits.

Discussion

This was the largest retrospective study to examine both AKI and intraoperative blood product administration in cardiac surgical patients receiving HES. The principal finding of this study illustrated no difference in AKI in patients who received colloid versus those who did not. Patients in the HES group also were not administered more red blood cell product than were patients in the non-HES group.

AKI After HES Use

AKI is associated with many complications after CPB, such as infections, increased mortality, and length of stay.[22] Longer CPB time also is associated with increased risk of AKI[23]; therefore, it is important to avoid factors that may worsen AKI after CPB. Two observational studies showed a dose-dependent decrease in the glomerular filtration rate in patients who received HES 450/0.7 and increased AKI in patients who received HES 200/0.5, respectively.[24,25] The former studied a different HES and defined AKI as glomerular filtration rate R assessment 3-to-5 days postoperatively, which differed from the STS criteria used for the study presented here and which

Table 3
Colloids Effects on AKI for CKD Stages 1-4

		n (%)	Observed AKI	
			n (%)	p Value
CKD Stages 1-4 Combined				
Intraoperative colloids	No	346 (28.6)	25 (7.5)	0.481
	Yes	865 (71.4)	53 (6.1)	
Intraoperative colloids	0) No HES	346 (28.6)	26 (7.5)	0.656
	1) < 1,000	406 (33.5)	27 (7.0)	
	2) ≥ 1,000	459 (37.5)	26 (6.7)	
Voluven	No Voluven	346 (40.7)	25 (7.2)	0.477
	1) < 1,000	204 (24.0)	14 (6.9)	
	2) 1,000	301 (35.4)	15 (5.0)	
Hextend	No Hextend	346 (49.0)	25 (7.2)	0.940
	1) 1,000	202 (28.6)	13 (6.4)	
	2) 1,000	158 (22.4)	11 (7.0)	
CKD stage 1: > 90				
Intraoperative colloids	No	62 (25.2)	2 (3.3)	0.642
	Yes	184 (74.8)	4 (2.2)	
Intraoperative colloids	0) No HES	62 (25.2)	2 (3.3)	0.716
	1) < 1,000	78 (31.7)	1 (1.3)	
	2) ≥ 1,000	106 (43.1)	3 (2.8)	
Voluven	No Voluven	62 (34.6)	2 (3.2)	0.922
	1) < 1,000	40 (22.4)	1 (2.5)	
	2) ≥ 1,000	77 (43.0)	3 (3.9)	
Hextend	No Hextend	62 (48.1)	2 (3.2)	0.334
	1) < 1,000	38 (29.5)	0	
	2) ≥ 1,000	29 (22.5)	0	
CKD stage 2: 60-89				
Intraoperative colloids	No	165 (26.2)	9 (5.5)	0.197
	Yes	466 (73.8)	15 (3.2)	
Intraoperative colloids	0) No HES	165 (26.2)	9 (5.5)	0.269
	1) < 1,000	218 (34.6)	5 (2.3)	
	2) ≥ 1,000	248 (39.3)	10 (4.0)	
Voluven	No Voluven	165 (37.8)	9 (5.5)	0.186
	1) < 1,000	111 (25.4)	2 (1.8)	
	2) ≥ 1,000	161 (36.8)	4 (2.5)	
Hextend	No Hextend	165 (45.9)	9 (5.5)	0.404
	1) < 1,000	107 (29.8)	3 (2.8)	
	2) ≥ 1,000	87 (24.2)	6 (6.9)	
CKD stage 3: 30-59				
Intraoperative colloids	No	106 (34.7)	11 (10.4)	0.209
	Yes	199 (65.3)	31 (15.6)	
Intraoperative colloids	0) No HES	106 (34.7)	11 (10.4)	0.259
	1) < 1,000	99 (32.5)	18 (18.2)	
	2) ≥ 1,000	100 (32.8)	13 (13.0)	
Voluven	No Voluven	106 (50.0)	11 (10.4)	0.485
	1) < 1,000	46 (21.7)	8 (17.4)	
	2) ≥ 1,000	60 (28.3)	8 (13.3)	
Hextend	No Hextend	106 (53.3)	11 (10.4)	0.324
	1) < 1,000	53 (26.6)	10 (18.9)	
	2) ≥ 1,000	40 (20.1)	5 (12.5)	
CKD stage 4: 15-29				
Intraoperative colloids	No	13 (44.8)	3 (23.1)	0.775
	Yes	16 (55.2)	3 (18.7)	
Intraoperative colloids	0) No HES	13 (44.8)	3 (23.1)	0.440
	1) < 1,000	11 (37.9)	3 (27.3)	
	2) ≥ 1,000	5 (17.2)	0	
Voluven	No Voluven	13 (56.5)	3 (23.1)	0.343
	1) < 1,000	7 (30.4)	3 (42.9)	
	2) ≥ 1,000	3 (13.0)	0	
Hextend	No Hextend	13 (68.4)	3 (23.1)	0.44
	1) < 1,000	4 (21.1)	0	
	2) ≥ 1,000	2 (10.5)	0	

NOTE. p value < 0.05 considered statistically significant. Total patients in this table did not add up to the total of 1,265 included in the study due to CKD 5 patients being omitted.

AKI, acute kidney injury; CKD, chronic kidney disease; HES, hydroxyethyl starches.

recorded peak Cr throughout the postoperative course. The latter study used a 10% solution that now rarely is available in the United States and Europe[26] and used different AKI criteria. The AKI results of the study presented here were similar to those of the meta-analysis that assessed smaller randomized, controlled trials (10 of the 19 included studies were cardiac surgery), which did not show a difference in AKI in surgical patients who received HES.[1] The study presented here was unique in that the authors attempted to determine whether pre-existing kidney disease worsened as a result of colloid administration and found the results not to be significantly different between various CKD stages. This study's data overall supported no correlation between these synthetic colloids and the development of AKI in cardiac surgery.

Blood Product Administration After HES Use

Patients in the colloid group did not receive more red blood cells intraoperatively or postoperatively compared with patients in the noncolloid group; instead, they received less PRBC than those in the noncolloid group. A previous review article containing smaller studies that covered 20 trials totaling 2,151 patients consisting mainly of cardiac, major abdominal, and orthopedic surgeries, did not find increased allogeneic erythrocyte transfusion in patients who received HES.[2] All included studies involved tetrastarches. Studies in cardiac surgery have shown a decreased clot formation rate and strength in patients who received primarily large-molecular-weight and molar-substitution HES, but the same studies did not examine blood product transfusion.[27-29] In studies that examined blood product administration, results have been conflicting. There have been reports of decreased blood loss and transfusion of PRBC in patients treated with rapidly degradable HES.[30,31] Increased blood loss and transfusions, however, also have been reported in studies that used purely higher-molecular-weight and molar-substitution HES.[32,33] After dividing the data between the higher-molecular-weight Hextend and the lower-molecular-weight Voluven in the study presented here, increased PRBC transfusion was not demonstrated with either product.

This study demonstrated an increased transfusion of FFP, cryo, and platelets, particularly in the high-volume HES group. Slowly degradable HES solutions with high molar substitution, such as Hextend, have been known to cause impaired coagulation via decreasing factor VIII and von Willebrand factor concentrations. These effects have not been shown with the use of rapidly degradable HES with low molar substitution and molecular weight, such as Voluven.[26,34,35] This slowly degradable effect of HES on coagulation could contribute partially to higher blood loss and increased blood product transfusion. Even though this study showed an overall increase in the administration of these blood products in the higher-volume HES group, the authors were unable to show significantly consistent high transfusion rates after dividing the colloid groups between Hextend and Voluven. Overall, using caution with higher HES volumes may seem reasonable in the presence of impaired coagulation.

Secondary Outcomes: Mortality, All-Cause Complications, and MACE

No difference in the surgical mortality in patients who received HES was observed; however, these results were not reproduced consistently in the subgroups of patients divided by Hextend and Voluven. The OR for surgical mortality was higher in the subgroup of patients who received Hextend < 1,000 mL. The wide confidence interval may have been due to outliers.

The increased OR of postoperative complications was significantly higher in both the high- and low-volume colloid groups. Similar significant results were observed in the divided colloid groups—Voluven and Hextend. To better define complications, MACE was used as a subcategory to enhance relevancy to the cardiac population. Interestingly, the MACE-adjusted ORs were higher in the low-volume colloid group and the low-volume Voluven group. The MACE-adjusted ORs were not significantly elevated in the high-volume colloid group. A possible explanation for this finding may have been that the low-volume colloid group received higher amounts of crystalloid administration, which has its own adverse effects such as those related to edema formation.[36]

Limitations

There were several limitations to this study, including the inability to randomize and blind that naturally coexist with retrospective studies. This also was a single-center study focused on a very specific patient population to lessen the burden of confounding variables that perturb retrospective studies. Although the take-home message is that HES is safe, clinicians may have selected patients without CKD when administering HES. However, propensity weighting was performed to take into consideration variables such as age, sex, race, surgery status, surgery type, cross-clamp time, bypass time, CKD stage, presence of other comorbidities, and medications, and adjusted ORs were calculated. Baseline anemia, which is a known risk factor for cardiac surgery-associated AKI, was not considered.[37] In addition, the authors were unable to control for the crystalloid and albumin administration. It may be possible that patients receiving lower HES received larger amounts of crystalloids that resulted in different outcomes. In retrospect, it also is important to consider the solution used to deliver the 2 types of HES that were used in this study. Whereas Hextend is suspended in a balanced salt solution, Voluven is suspended in saline. The difference of chloride in these 2 products that may have contributed to AKI was not considered. Also, other confounding variables may have formed after dividing the patient population by colloid types. For example, Hextend mainly was used from 2007 to 2009 at the authors' institution, and a transition to Voluven occurred from 2009 to 2013.

The AKI criteria in this study also differed from the criteria of the Acute Kidney Injury Network and RIFLE (Risk, Injury, Failure, Loss of function, End-stage kidney disease), 2 popular criteria used to measure AKI.[38,39] The STS definition is a more stringent definition adapted and modified from the Failure Stage of the RIFLE criteria. The length of Cr monitoring also differed because the Acute Kidney Injury Network uses a 48-hour window to measure Cr, RIFLE uses a 7-day window,[39] and STS criteria use the entire postoperative period. Various heterogenous criteria made it difficult to compare AKI results among studies. In addition, long-term CKD development and long-term mortality were not examined.

Conclusions

In conclusion, no differences in the development of postoperative AKI and administration of PRBC products between the colloid and noncolloid groups were demonstrated. Due to an increase in other blood product administration and an increase in postoperative complications noted with the colloid group, randomized prospective studies are needed in this population to draw more definite conclusions about HES safety and long-term effects.

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