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Clinical impact of disinvestment in hydroxyethyl starch for patients undergoing coronary artery bypass surgery: a retrospective observational study

Répercussions cliniques du déclin de l'utilisation de l'amidon hydroxyéthile chez les patients subissant un pontage coronarien : une étude observationnelle rétrospective

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Abstract

Purpose *To examine the effect of discontinuing hydroxyethyl starch (HES) solutions on length of hospital stay, transfusion, risk of death, acute kidney injury (AKI), and dialysis.*

Methods *We conducted a historical cohort study of linked administrative and clinical databases in patients undergoing coronary artery bypass surgery (CABG) on cardiopulmonary bypass. We used propensity scores to match patients who did not receive HES (after discontinuation) with patients exposed to HES (before discontinuation) and also controlled for albumin exposure. Hospital length of stay (the primary outcome) was analyzed using Fine-Gray proportional hazard regression, with hospital discharge as the outcome and death as a competing risk. Adverse outcomes were compared between matched patients using conditional logistic regression.*

Results *We compared 1,085 propensity score-matched pairs (n = 2,170) from a pool of 2,757 patients.*

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Discontinuation of HES was associated with shorter length of hospital stay, as evidenced by an increased probability of discharge (hazard ratio, 1.24; 95% confidence interval [CI], 1.14 to 1.35) and a reduced risk of red blood cell transfusion (odds ratio [OR], 0.68; 95% CI, 0.55 to 0.84), plasma transfusion (OR, 0.48; 95% CI, 0.34 to 0.66), and platelet transfusion (OR, 0.62; 95% CI, 0.44 to 0.87). Discontinuation of HES was not associated with in-hospital mortality (OR, 0.74; 95% CI, 0.36 to 1.54), AKI (OR, 0.84; 95% CI, 0.57 to 1.25), or dialysis (OR, 0.83; 95% CI, 0.25 to 2.73).

Conclusions *For patients undergoing CABG on cardiopulmonary bypass, discontinuation of HES was associated with reduced hospital length of stay and reduced blood product transfusion, without measurable change in renal failure, dialysis rate, or in-hospital mortality. Our results should be interpreted with caution, though we found no evidence of harms associated with discontinuing HES.*

Trial registration *www.clinicaltrials.gov (NCT02329158); registered 31 December, 2014.*

Résumé

Objectif *Étudier les répercussions de l'arrêt des solutions d'amidon hydroxyéthile (HEA) sur la durée de séjour à l'hôpital, les transfusions, le risque de décès, les lésions rénales aiguës (LRA) et la dialyse.*

Méthodes *Nous avons réalisé une étude de cohorte historique dans des bases de données liées, administratives et cliniques, sur des patients subissant une chirurgie de pontage coronarien sous circulation extracorporelle. Nous avons utlisé des scores de propension pour apparier des patients qui n'avaient pas reçu de HEA (après son arrêt) à des patients exposés au HEA (avant son arrêt) et avons également contrôlé l'exposition à l'albumine. La durée du séjour à l'hôpital (principal critère d'évaluation) a été analysée au moyen d'un modèle de régression proportionnelle du risque de Fine-Gray en utilisant le congé de l'hôpital comme aboutissement et le décès comme risque compétitif. Les évolutions défavorables ont été comparées entre patients appariés en utilisant un modèle de régression logistique conditionnelle.*

Résultats *Nous avons comparé 1 085 paires de patients (n = 2 170) appariés en fonction du score de propension à partir d'une population de 2 757 patients. L'arrêt du HEA a été associé à une plus courte durée de séjour à l'hôpital, comme l'a montré une augmentation de la probabilité de congé (rapport de risque, 1,24; intervalle de confiance [IC] à 95 % : 1,14 à 1,35) et une baisse du risque de transfusion de globules rouges (rapport de cotes [OR], 0,68; IC à 95 %, 0,55 à 0,84), de transfusion de plasma (OR, 0,48; IC à 95 %, 0,34 à 0,66) et de plaquettes (OR, 0,62; IC à 95 %, 0,44 à 0,87). L'arrêt du HEA n'a pas été associé à la mortalité au cours de l'hospitalisation (OR, 0,74; IC à 95 %, 0,36 à 1,54), des LRA (OR, 0,84; IC à 95 %, 0,57 à 1,25) ou la dialyse (OR, 0,83; IC à 95 %, 0,25 à 2,73).*

Conclusions *Pour les patients subissant un pontage coronarien sous circulation extracorporelle, l'arrêt du HEA a été associé à un raccourcissement de la durée de séjour à l'hôpital et à une diminution des transfusions de produits sanguins sans différence mesurable sur les taux d'insuffisance rénale, de dialyse ou de mortalité hospitalière. Nos résultats doivent être interprétés avec prudence bien que nous n'ayons pas trouvé de données probantes d'effets nuisibles associés à l'arrêt du HEA.*

Enregistrement de l'essai clinique *www.ClinicalTrials.gov (NCT02329158). Enregistré le 31 décembre 2014.*

Health Canada guidelines recommend against the use of hydroxyethyl starch (HES) for critically ill patients, specifically patients with sepsis, severe liver disease, or impaired kidney function.[1–3] In many institutions, use of HES has been reduced in the critical care setting, but has continued in the perioperative setting based on the belief that surgical patients may be less susceptible to the adverse effects of HES than critically ill patients.[4-6] This perception is likely due to surgical patients typically having a shorter duration of exposure and a lower risk of organ dysfunction. In general, perioperative options for fluid replacement include red blood cell (RBC) transfusion, colloid solutions (e.g., HES, gelatins, and albumin), and crystalloid solutions (e.g., Ringer's lactate and saline).

Prior to 2 April 2013, HES was administered to all patients undergoing cardiopulmonary bypass (CPB) surgery at the London Health Sciences Centre (LHSC). In some cases, HES was also administered following surgery. A systematic review and meta-analysis conducted by the Centre for Medical Evidence, Decision Integrity & Clinical Impact (MEDICI), and presented to the hospital pharmacy and therapeutics committee, showed that patients exposed to HES as fluid replacement therapy were at greater risk of death, renal replacement therapy, and blood product transfusion compared with patients not exposed to HES (institutional report, unpublished data). Therefore, on 2 April 2013, LHSC chose to discontinue the use of HES for fluid replacement therapy across the entire institution as the risks for all patients appeared to outweigh potential benefits for any patient group. After disinvestment, the options for fluid replacement therapy at LHSC were normal saline, Ringer's lactate, albumin, and blood products. The volume of HES used in the CPB priming fluid pre-disinvestment was replaced with Ringer's lactate post-

disinvestment. This disinvestment formed the basis of a natural experiment allowing us to investigate the clinical impact of the decision, comparing patient outcomes before *vs* after discontinuing use of HES at our institution. This natural experiment provided an HES-exposed (prior to 2 April 2013) *vs* non-HES-exposed (after 2 April 2013) population for comparison.

Accordingly, we performed a historical cohort study to compare two eras of patients undergoing coronary artery bypass graft surgery (CABG): patients from the pre-disinvestment period who were all exposed to HES and patients from the post-disinvestment period who were never exposed to HES. Our hypothesis was that patients from the non-HES group would have no difference in hospital length of stay and no difference in risk of adverse events than patients from the HES group.

Methods

The University of Western Ontario Research Ethics Board approved the study (15 May 2015) and waived the requirement for patient informed consent. The study was registered on ClinicalTrials.gov (NCT02329158) prior to study initiation.

We conducted a historical analysis of linked administrative and clinical databases, in accordance with guidelines set by the REporting of studies Conducted using Observational Routinely-collected Data statement.[7] Results were reported according to provisional guidelines for propensity-matched observational studies.[8]

To select the study cohort, we used a database maintained by LHSC clinical perfusionists to identify all adults who underwent a cardiac surgical procedure with CPB between 1 April 2011 and 31 May 2015 at LHSC. The first era was defined as 1 April 2011 to 31 March 2013, prior to disinvestment in HES, while the second era, the post-disinvestment era, was defined as 1 June 2013 to 31 May 2015. The dates were chosen to incorporate two years prior to disinvestment and two years after disinvestment and based on the availability of data. We implemented a two-month washout period between 1 April 2013 and 31 May 2013 to ensure HES had been completely removed from the hospital prior to the second era of the study. All patients in the first era were exposed to HES for fluid replacement therapy, because the standard CPB priming solution consisted of 1 L Ringer's lactate, 200 mL 20% mannitol, and 500 mL 6% HES 130/0.4 (Voluven® Fresenius Kabi). In the post-disinvestment second era, HES was replaced with Ringer's lactate, and the priming solution consisted of 1.5 L Ringer's lactate and 200 mL 20% mannitol (Fig. 1). Patients may have received allogeneic blood products and additional colloid and crystalloid fluids as ordered by the physician caring for the patients. Patients in both eras, pre- and post-disinvestment, were exposed to crystalloid solutions.

We obtained person-level data from administrative and clinical databases including: 1) the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), 2) the Cardiac Care Network (CCN) database, 3) the Department of Cardiovascular and Thoracic Surgery's Cardiac Surgery Database, 4) Clinical Perfusion Services' cardiopulmonary bypass records, 5) LHSC blood transfusion records, and 6) data from the electronic medical record at LHSC. The data were anonymized by assigning a unique personal identification number (PIN) to replace the Ontario Health Insurance Plan number. All databases were securely linked using the anonymized PIN or hospital identification number.

Validation of the linkage was conducted for the DAD and CCN database. For a random sample of 150 subjects from the study cohort, we compared date of birth and sex between each database. Demographic data from the DAD was previously validated by the Institute for Clinical Evaluative Sciences, with high agreement between the original coder and reabstractor.[9]

This study included all patients (age $\geq$ 18 yr) who underwent on-pump CABG, with or without replacement or repair of the mitral valve, aortic valve, or both the mitral and aortic valves. We included only the first instance of CABG surgery within the study period. We excluded patients enrolled in the "Volulyte^{TM} in Cardiac Surgery" trial (ClinicalTrials.gov identifier: NCT01553617), as the study period overlapped with the pre- and post-disinvestment eras.[10] We excluded patients admitted, discharged, or both admitted and discharged during the washout period (1 April 2013 to 31 May 2013). We also excluded patients with a prior history of dialysis.

The primary outcome was the length of hospital stay. Secondary outcomes were in-hosptial mortality, acute kidney injury (AKI), new-onset renal dialysis, and blood product transfusion, including RBCs, plasma, or platelets. The length of hospital stay was recorded as the difference between the admission date and discharge date, in days. The definition of AKI used the modified KDIGO (Kidney DiseaseImproving Global Outcomes) criteria.[11] We compared peak serum creatinine seven days after surgery with the preoperative creatinine measurement with AKI defined as an increase in serum creatinine by $\geq$ 0.3 mg·dL^{-1} (26.5 μmol·L^{-1}), an increase to $\geq$ 1.5 times preoperative levels, or requirement for in-hospital dialysis. Urine output information was not recorded in the databases, so this KDIGO criterion for AKI was not included. Cost of hospitalization was a secondary outcome

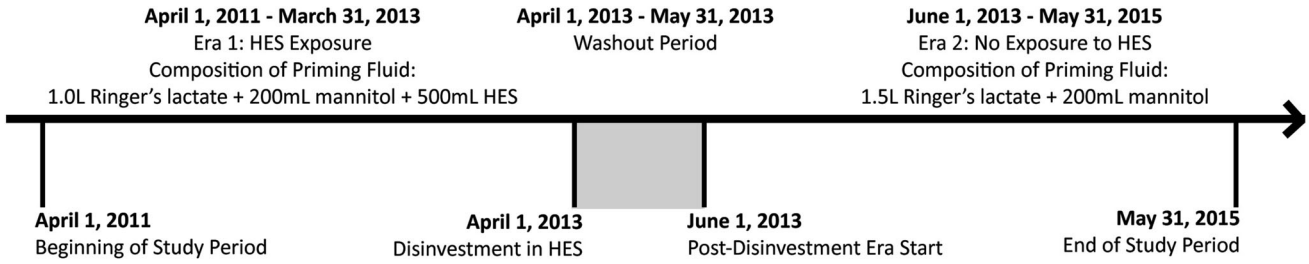

Fig. 1 Study timeline and composition of the fluid priming solution. *HES* hydroxyethyl starch

specified in our trial registration, which we will address in a subsequent research publication.

Statistical analysis

Descriptive statistics are presented as mean (standard deviation [SD]) for continuous variables, number (percentage) for categorical variables, and standardized differences and *P* values for comparison between exposure groups. We adjusted for baseline covariates expected to be associated with outcomes, including patient age, sex, body mass index (BMI), CPB time, number of cardiac valves operated on, urgency of operation, Canadian Cardiovascular Society (CCS) and acute coronary syndrome (ACS) class, left ventricular ejection fraction (LVEF) category, baseline creatinine, surgeon, previous CABG or percutaneous coronary intervention, and history of diabetes, using a propensity score.

Missing values were imputed using a randomly selected value from other observations. The variable with the largest number of missing observations was the LVEF category, with only 55 missing observations (less than 2% of the data set). Missing observations were also found for BMI (13 patients), CCS/ACS class (nine patients), and history of diabetes (nine patients).

Propensity scores were obtained by logistic regression, modelling the exposure to HES as the dependent variable with all of the above baseline covariates as independent variables. For each patient, the propensity score for those treated in the first era was matched to those treated in the second era in a 1:1 ratio, without replacement. Thus, one patient exposed to HES was matched to only one patient not exposed to HES. Patients were matched using the closest propensity score on the logit scale with a maximum difference of $\pm$ 0.025, equivalent to the recommended caliper size defined by 0.2 times the standard deviation of the logit of the propensity score.[12] Balance of covariates between treatment arms was assessed by comparing standardized differences of covariates between the matched and unmatched sample. Summary statistics were calculated for each treatment group in the unmatched and matched sample. After controlling for baseline covariates using propensity score methods, we controlled for the effect of albumin use during surgery or during the postoperative period.

We evaluated the difference in length of hospital stay between the two eras using Fine-Gray proportional hazard regression to model time to discharge alive with death as a competing risk and censoring transfer to another institution. This approach censored patients who died while accounting for length of hospital stay. Simply censoring patients who died may have led to informative censoring and biased estimates.[13] Cluster-robust standard errors were used to account for the lack of independence between paired data. The proportional hazards assumption was assessed by examining the plot of the log of the negative log of the estimated survivor function against the log of time. Conditional logistic regression was conducted on the matched pairs to assess the effect of disinvestment on dichotomous outcomes, controlling for albumin. *P* values were two sided and values < 0.05 were considered statistically significant. Sensitivity analyses were conducted comparing the effect of only study era on outcomes and also using the effect of study era, albumin, and the interaction between the two covariates. Additional sensitivity analyses were conducted for each binary outcome using inverse probability of exposure weighting for the entire data set, controlling for the effect of study era, the effect of study era and albumin, and the effect of study era, albumin, and the interaction between the two. Regression estimates are reported along with 95% confidence intervals (CI).

Analyses were performed using SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) and the software R for statistical computing with the 'survival' and 'cmprsk' packages.[14-16]

Results

A total of 3,030 CABG procedures were performed during the study period. One hundred sixty-six operations were excluded from the study because the patients had been admitted, discharged, or both admitted and discharged

during the two-month washout period. Eleven patients were excluded for participating in the "Volulyte™ in Cardiac Surgery" trial. In addition, 44 patients were excluded for having a history of dialysis, and 52 patients who had repeat procedures that fell within the study period were also excluded. Following these 273 exclusions, the study cohort included 2,757 patients, with 1,496 patients exposed to HES and 1,261 patients not exposed to HES (Fig. 2). In the unmatched cohort, non-HES patients were more likely to have previously undergone cardiac surgery and to have been exposed to albumin transfusion during the hospital stay (Table 1). There were also significant differences in CCS/ACS class and the operating surgeon. Among the unmatched sample, the mean (SD) length of stay for non-HES patients was 10.6 (10.4) days, while the mean (SD) length of stay for HES patients was 11.2 (10.7) days. The frequency of binary outcomes between the groups is reported in Table S1 (available as Electronic Supplementary Material [ESM]). Validation of linkage between the CCN and CIHI databases showed that 148 of the 150 (99%) randomly sampled subjects matched by date of birth and sex.

Propensity score matching resulted in 1,085 of the 1,261 patients not exposed to HES being matched with 1,085 of 1,496 patients exposed to HES. Table 2 reports the baseline characteristics and standardized differences between the matched pairs. Propensity score matching excluded patients with the highest likelihood of receiving only crystalloids. After matching by propensity score, the mean propensity score between treatment arms was equal, standardized differences between groups were lower for all variables except for age and BMI, and P values were larger, except for age and the number of valves operated on.

As for the primary outcome, among the matched sample, the mean (SD) length of hospital stay for patients not exposed to HES was 10.6 (10.5) days compared with 11.1 (10.1) days in the HES group. After accounting for the competing risk of death and adjusting for exposure to albumin during the hospital stay, patients exposed to HES were less likely to be discharged from hospital at each moment in time than patients not exposed to HES (subhazard ratio for length of hospital stay, 1.24; 95% CI, 1.14 to 1.35; $P < 0.001$) (Table 3). The cumulative probability of being discharged alive was consistently higher in the non-HES group than in the HES group, and the cumulative probability of in-hospital mortality was consistently lower in the non-HES group than in the HES group. Albumin exposure was associated with a significantly lower likelihood of being discharged alive, suggesting albumin exposure was associated with longer length of hospital stay. Additional analysis did not find a significant relationship between date of operation and length of hospital stay when controlling for all baseline variables included in the propensity score model and the treatment era variable (Table S2, available as ESM). Nevertheless, in this sensitivity analysis, patients who were not exposed to HES no longer had significantly shorter

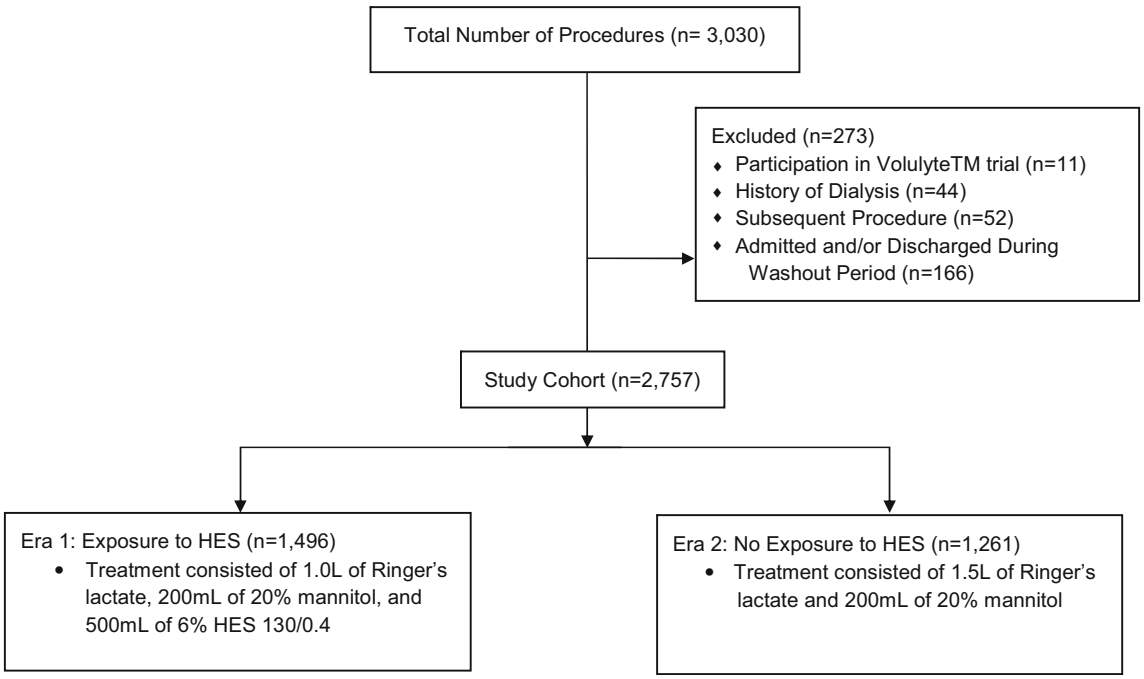

Fig. 2 CONSORT diagram for inclusion and exclusion of patients into the study

Table 1 Selected baseline characteristics of the study population, stratified by intervention, before matching

Variable	HES (n = 1,496)	Non-HES (n = 1,261)	Standardized difference (%)	Comparison (P value)
Age	66.9 (10.2)	67.2 (9.8)	2.98	0.44
Body mass index	29.6 (5.3)	29.5 (5.5)	0.70	0.70
Female	306 (20.5%)	286 (22.7%)	4.45	0.16
Diabetes on admission	534 (35.7%)	486 (38.5%)	4.82	0.12
Previous cardiac surgery	161 (10.8%)	175 (13.9%)	7.89	0.01
Urgent surgery	748 (50.0%)	650 (51.6%)	2.53	0.42
Valve†				0.79
0	1,253 (83.8%)	1067 (84.6%)		
1, 2	243 (16.2%)	194 (15.4%)		
Left ventricular ejection fraction category				0.97
1 (≥ 50%)	911 (60.9%)	768 (60.9%)		
2 (35-49%)	410 (27.4%)	349 (27.7%)		
3 (20-34%)	144 (9.6%)	121 (9.6%)		
4 (< 20%)	31 (2.1%)	23 (1.8%)		
Albumin transfusion	172 (11.5%)	342 (27.1%)	34.89	< 0.001
Pump time (min)	97.0 (42.3)	94.1 (44.3)	6.71	0.08
Baseline creatinine ($\mu mol \cdot L^{-1}$)	89.0 (36.1)	88.6 (39.0)	1.27	0.74
CCS/ACS Class				0.0085
0	139 (9.3%)	119 (9.4%)		
1	96 (6.4%)	81 (6.4%)		
2	301 (20.1%)	237 (18.8%)		
3	305 (20.4%)	278 (22.1%)		
4	15 (1.0%)	16 (1.3%)		
Emergent	30 (2.0%)	15 (1.2%)		
Low	171 (11.4%)	202 (16.0%)		
Intermediate	384 (25.7%)	274 (21.7%)		
High	55 (3.7%)	39 (3.1%)		
Surgeon‡				< 0.001
1	195 (13.0%)	127 (10.1%)		
2	166 (11.1%)	87 (6.9%)		
3	47 (3.1%)	26 (2.1%)		
4	242 (16.2%)	157 (12.5%)		
5	217 (14.5%)	219 (17.4%)		
6	117 (7.8%)	60 (4.8%)		
7	27 (1.8%)	128 (10.2%)		
8	269 (18.0%)	236 (18.7%)		
9	216 (14.4%)	221 (17.5%)		

ACS = acute coronary syndrome; CCS = Canadian Cardiovascular Society; HES = hydroxyethyl starch. Results are expressed as either mean (standard deviation) or number (percentage). †Patients have been grouped for reporting purposes. ‡Surgeons have been anonymized

length of hospital stay (subhazard ratio for length of hospital stay, 1.07; 95% CI, 0.90 to 1.26; P = 0.45) (Table S2, available as ESM).

After matching by propensity score and adjusting for albumin exposure in a conditional logistic regression model, patients not exposed to HES had a statistically significantly lower risk of RBC, plasma, and platelet transfusion compared with their matched counterparts who were exposed to HES (Table 4). Reductions in risk of in-hospital mortality, AKI, and dialysis were not statistically

Table 2 Selected baseline characteristics of the study population, stratified by intervention, after matching*

Variable	HES (n = 1,085)	Non-HES (n = 1,085)	Standardized difference (%)	Comparison (P value)
Age	66.5 (10.1)	67.0 (9.9)	4.95	0.25
Body mass index	29.4 (5.2)	29.5 (5.5)	1.50	0.73
Female	240 (22.1%)	230 (21.2%)	1.82	0.60
Diabetes on admission	410 (37.8%)	394 (36.3%)	2.49	0.48
Previous cardiac surgery	139 (12.8%)	139 (12.8%)	0.00	1.00
Urgent surgery	566 (52.2%)	553 (51.0%)	1.96	0.58
Valve†				0.77
0	926 (85.4%)	914 (84.2%)		
1, 2	160 (14.6%)	171 (15.8%)		
Left ventricular ejection fraction category				0.99
1 (≥ 50%)	667 (61.5%)	672 (61.9%)		
2 (35-49%)	294 (27.1%)	291 (26.8%)		
3 (20-34%)	104 (9.6%)	101 (9.3%)		
4 (< 20%)	20 (1.8%)	21 (1.9%)		
Albumin transfusion	125 (11.5%)	298 (27.5%)	35.52	< 0.001
Pump time (min)	94.2 (34.8)	94.2 (42.4)	0.02	0.997
Baseline creatinine ($\mu mol \cdot L^{-1}$)	89.2 (35.8)	89.3 (39.6)	0.38	0.93
CCS/ACS class				1.00
0	103 (9.5%)	105 (9.7%)		
1	72 (6.6%)	73 (6.7%)		
2	206 (19.0%)	214 (19.7%)		
3	229 (21.1%)	227 (20.9%)		
4	14 (1.3%)	13 (1.2%)		
Emergent	15 (1.4%)	15 (1.4%)		
Low	149 (13.8%)	145 (13.4%)		
Intermediate	262 (24.2%)	257 (23.7%)		
High	35 (3.2%)	36 (3.3%)		
Surgeon‡				0.998
1	118 (10.9%)	123 (11.3%)		
2	92 (8.5%)	87 (8.0%)		
3	27 (2.5%)	27 (2.5%)		
4	164 (15.1%)	157 (14.5%)		
5	198 (18.3%)	189 (17.4%)		
6	58 (5.4%)	59 (5.4%)		
7	26 (2.4%)	27 (2.5%)		
8	222 (20.5%)	224 (20.7%)		
9	180 (16.6%)	192 (17.7%)		

ACS = acute coronary syndrome; CCS = Canadian Cardiovascular Society; HES = hydroxyethyl starch. Results are expressed as either mean (standard deviation) or number (percentage)

*Patients were matched using propensity score adjusted for age, sex, body mass index, pump time (min), number of valves operated on, urgency of operation, Canadian Cardiovascular Society and acute coronary syndrome class, left ventricular ejection fraction category, baseline creatinine, surgeon, previous cardiopulmonary bypass surgery or percutaneous coronary intervention, and history of diabetes. †Patients have been grouped for reporting purposes. ‡Surgeons have been anonymized

significant (Table 4). Albumin exposure was associated with a higher risk of RBC, plasma and platelet transfusion, AKI, and in-hospital mortality. Sensitivity analyses show our findings are robust to model specification and risk-adjustment method (ESM Tables).

Table 3 Competing-risks regression for effects of HES and albumin on hospital length of stay (n = 2,170)*

Outcome	Covariate	Subhazard ratio (95% CI)	P value
Discharge	Non-HES	1.24 (1.14 to 1.35)	< 0.001
	Albumin	0.43 (0.39 to 0.48)	< 0.001
Death	Non-HES	0.48 (0.26 to 0.89)	0.02
	Albumin	12.88 (6.43 to 25.81)	< 0.001

CI = confidence interval; HES = hydroxyethyl starch

*Using the propensity-matched data (n = 1,085 HES exposed, n = 1,085 non-HES exposed), the difference in hospital length of stay between non-HES and HES was evaluated using Fine-Gray proportional hazard regression to model time to discharge alive with death as a competing risk, and censoring transfer to another institution, with additional control for albumin exposure. Cluster-robust standard errors were used to account for the lack of independence between paired data

Table 4 Conditional logistic regression for effects of HES and albumin (n = 2,170)*

Outcome	Covariate	Odds ratio (95% CI)	P value
Mortality	Non-HES	0.74 (0.36 to 1.54)	0.42
	Albumin	13.04 (8.83 to 19.48)	< 0.001
RBC transfusion	Non-HES	0.68 (0.55 to 0.84)	< 0.001
	Albumin	6.00 (4.00 to 8.99)	< 0.001
Plasma transfusion	Non-HES	0.48 (0.34 to 0.66)	< 0.001
	Albumin	8.50 (4.76 to 15.18)	< 0.001
Platelet transfusion	Non-HES	0.62 (0.44 to 0.87)	0.006
	Albumin	7.38 (3.93 to 13.86)	< 0.001
AKI	Non-HES	0.84 (0.57 to 1.25)	0.39
	Albumin	4.34 (2.39 to 7.89)	< 0.001
Dialysis	Non-HES	0.83 (0.25 to 2.73)	0.76
	Albumin	> 999 (<0.001 to > 999)	0.995

AKI = acute kidney injury; CI = confidence interval; HES = hydroxyethyl starch; RBC = red blood cell

*Using the propensity-matched data (n = 1,085 HES exposed, n=1,085 non-HES exposed), conditional logistic regression was conducted to assess the effect of non-HES compared with HES on dichotomous outcomes, controlling for albumin

Discussion

In this propensity-matched historical cohort study of patients undergoing CABG surgery on CPB, we identified significant reductions in length of hospital stay and blood product transfusion (RBCs, plasma, and platelets) following institution-wide disinvestment in HES. Changes in in-hospital mortality, AKI, and dialysis following disinvestment in HES were not significant. Disinvestment in HES did not increase mortality and renal failure, which was a concern expressed by clinicians because of assumptions of excess risk from replacing HES with crystalloids when the policy of withdrawal of HES from the institution was implemented. Given the challenges associated with historical cohort studies, we urge caution in the interpretation of our results. Nevertheless, using a variety of analytic methods and risk-adjustment models, we did not observe harms associated with discontinuing HES.

Our findings are consistent with those of Bayer *et al.* who conducted a prospective sequential analysis of HES disinvestment in the cardiac intensive care unit (ICU).[17] In their propensity-score adjusted analysis, HES was associated with increased odds of renal replacement therapy compared with crystalloids only (odds ratio, 1.46; 95% CI, 1.08 to 1.97). Our findings of decreased length of hospital stay contradict the findings of one meta-analysis that found exposure to HES was associated with a shorter length of hospital stay than exposure to crystalloid solutions alone; the meta-analysis did not account for mortality through competing risks analysis as in our study.[18] Our findings are consistent with results of other meta-analyses focused on cardiac surgical patient groups that found HES exposure was associated with increased risk of transfusion.[18-20] Although mortality, AKI, and dialysis effect estimates were not statistically significant, our results are consistent in both the direction and

magnitude of effect with meta-analyses of clinical trials of perioperative patient populations that found HES to be associated with an increased risk of mortality, AKI, renal replacement therapy, and blood product transfusion.[4-6,21,22]

Regarding the potential confounding effect of albumin, our findings of significant increases in length of hospital stay, blood product transfusions, and mortality associated with albumin exposure are difficult to interpret in the context of HES disinvestment. Our extensive sensitivity analyses in which the risk-adjustment method and risk-adjustment variables were changed show consistent evidence that disinvestment in HES was associated with improved outcomes, but that albumin exposure was independently associated with harms. The harms associated with albumin and HES may represent a colloid class effect, which was difficult to accurately attribute to each colloid without data on the timing and amount of colloid administration. Nevertheless, meta-analyses comparing albumin to crystalloids suggest no significant difference in harm in the ICU setting.[21,23] Thus, albumin exposure in our study may be a proxy of unmeasured confounders, and these may have differed pre- and post-disinvestment. Prior to disinvestment, albumin exposure may have been a marker of "sicker" patients (hypoalbuminemic or hemodynamic instability leading to concomitantly increased volume or duration of exposure to HES), while post-disinvestment use of albumin for sicker patients would not have been associated with increased HES exposure.

Our study has some limitations inherent to observational analyses. Although our approach to propensity score modelling controlled for differences in patient-level characteristics between the two eras, we cannot be certain if changes in outcome were due to unmeasured temporal changes in care. Indeed, in a sensitivity analysis controlling for the date of surgery, the association between non-HES exposure and shorter length of hospital stay was no longer significant (ESM Tables). Due to the interrelated nature of HES exposure and time, we urge caution in interpreting this sensitivity analysis. Adjusting for temporal changes in length of hospital stay may represent over adjustment. In other words, decreasing length of stay over time could have been caused, at least in part, by disinvestment in HES, and thus adjusting for surgery date would be adjusting for a variable in the causal pathway. We acknowledge the limitations of our retrospective observational study to definitively quantify the effect of HES disinvestment given the difficulties of adjusting for temporal changes in length of hospital stay. Nevertheless, despite using different risk-adjustment models and different analytic approaches, the one thing we did not observe was harm associated with non-HES exposure.

The potential for misclassification bias was also a limitation. Post-disinvestment of HES, misclassification of exposure was not possible because the institution completely discontinued purchasing the fluid. Nevertheless, prior to discontinuation of HES, our clinical perfusionists estimate that for one or two patients each year, a treating clinician may have requested that HES be removed from the CPB priming fluid; therefore, it is possible that exposure to HES was misclassified for a very small number of patients in the first era. Unfortunately, our institution is typical of most Canadian hospitals in that we do not keep electronic records of the volume of fluids administered; thus, we were not able to investigate a dose-response relationship between HES exposure and adverse clinical outcomes. We defined length of hospital stay from the date of admission to the date of discharge and did not analyze postoperative length of stay. Nevertheless, admission and procedure dates were identical for more than 96% of patients in our data set. All observational studies, including propensity score analyses, are subject to residual confounding by unmeasured variables. For example, we did not have complete electronic data on preoperative hemoglobin, and anemia may have played a role in the type and volume of fluids administered. Observational studies are also at risk of over-correction for potentially correlated clusters of variables. Therefore, we are careful not to directly ascribe a cause-effect relationship between discontinuation of HES and the clinical outcomes we observed. Nevertheless, the fact that our findings are consistent with previous studies suggests that a causal relationship is plausible.

We did not detect significant differences between dialysis and AKI between matched groups. Urine output changes are one criterion for measuring AKI by the KDIGO criteria. As is typical in most Canadian hospitals, urine output information is not routinely captured in electronic records; however, the additional predictive validity of urine output for cardiac surgical patients is questionable.

This study was conducted with the purpose of detecting whether discontinuation of HES as fluid replacement therapy was associated with patient harms. Nevertheless, disinvestment in HES was associated with shorter length of hospital stay and lower risk of allogeneic blood product transfusion, without increased risk of death or renal failure, suggesting that there may be clinically significant benefits to discontinuing HES. Our study was focused on patients undergoing CABG with CPB, but our findings may potentially be generalizable to other surgical patients, given the strong evidence of harms in ICU patients and patients with sepsis shown by systematic reviews.[2,24] The significant association we discovered between albumin exposure and harms may be interpreted by some as indirect

evidence of harm associated with disinvestment in HES, which may increase the use of albumin. Nevertheless, in the absence of external evidence to confirm harms associated with albumin, this would be a misinterpretation or projection of our study findings. Multiple randomized trials of albumin *vs* other colloids and crystalloids have failed to show net harm from albumin, and the randomized trials should be relied upon to inform conclusions about albumin rather than our indirect analysis of the confounding effect of albumin in a retrospective manner.

Additional studies from centres discontinuing use of HES would be beneficial to further inform clinical and policy decisions. On 26 January 2018, the European Medicines Agency suspended the marketing authorizations of HES solutions across the European Union. This has sparked concerns about fluid resuscitation options for surgical patients in the absence of HES.[25,26] As more institutions discontinue use of HES, we hope that additional studies can further enlighten this debate. The net health benefit and overall cost impacts should be formally explored, since the reductions in clinically relevant adverse effects together with potential cost-saving from avoidance of HES relative to crystalloids indicates that the net cost savings may be substantial.[27] Analyses should also account for potential health impacts and cost increases from the use of other fluids, such as albumin. We plan to investigate the impact of disinvestment on hospitalization costs in a subsequent analysis.

In conclusion, for patients undergoing CABG on CPB, disinvestment in HES was associated with a reduced length of hospital stay and reduced blood product transfusion, without measurable change in death, renal failure, or dialysis rate. This association suggests that the continued use of HES in the cardiac surgical setting should be carefully reconsidered.

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Conflicts of interest None declared.

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