Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: A meta-analysis of randomized trials

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Objective: The effects of hydroxyethyl starch on bleeding after cardiopulmonary bypass were determined.

Methods: A meta-analysis was performed of postoperative blood loss in randomized clinical trials of hydroxyethyl starch versus albumin for fluid management in adult cardiopulmonary bypass surgery. Impacts of hydroxyethyl starch molecular weight and molar substitution were assessed. Randomized trials directly comparing different hydroxyethyl starch solutions were also included.

Results: Eighteen trials with 970 total patients were included. Compared with albumin, hydroxyethyl starch increased postoperative blood loss by 33.3% of a pooled SD (95% confidence interval, 18.2%–48.3%; $P < .001$). Risk of reoperation for bleeding was more than doubled by hydroxyethyl starch (relative risk, 2.24; 95% confidence interval, 1.14–4.40; $P = .020$). Hydroxyethyl starch increased transfusion of red blood cells by 28.4% of a pooled SD (95% confidence interval, 12.2%–44.6%; $P < .001$), of fresh-frozen plasma by 30.6% (95% confidence interval, 8.0%–53.1%; $P = .008$), and of platelets by 29.8% (95% confidence interval, 3.4%–56.2%; $P = .027$). None of these effects differed significantly between hydroxyethyl starch 450/0.7 and 200/0.5. Insufficient data were available for hydroxyethyl starch 130/0.4 versus albumin; however, no significant differences were detected in head-to-head comparisons of hydroxyethyl starch 130/0.4 with 200/0.5. Albumin improved hemodynamics. There were no differences in fluid balance, ventilator time, intensive care unit stay, or mortality.

Conclusions: Hydroxyethyl starch increased blood loss, reoperation for bleeding, and blood product transfusion after cardiopulmonary bypass. There was no evidence that these risks could be mitigated by lower molecular weight and substitution. (*J Thorac Cardiovasc Surg* 2012;144:223–30)

Supplemental material is available online.

Excessive postoperative bleeding remains a frequent, serious, and unpredictable complication of cardiac surgery with cardiopulmonary bypass (CPB) that can prompt transfusion of blood products, delay extubation, necessitate reoperation, and worsen outcome. CPB can result in acquired transient platelet dysfunction attended by diffuse nonsurgical postoperative bleeding. Choice of fluid for extracorporeal circuit priming and perioperative volume expansion may modify the risk of excessive coagulopathic

bleeding. Common choices are colloids such as albumin and hydroxyethyl starch (HES).

A 2001 meta-analysis of 16 randomized trials with 653 total patients undergoing surgery with CPB demonstrated an increase in postoperative blood loss among patients receiving HES relative to albumin.¹ A warning against the use of HES in cardiac surgery because of increased bleeding risk was thereafter required by the US Food and Drug Administration on the prescribing information for HES of molecular weight 450 kDa and molar substitution 0.7 (HES 450/0.7) in saline solution.

Nevertheless, HES solutions continue to be advocated for use in surgery with CPB. It has been postulated that HES solutions of lower molecular weight and substitution could carry less bleeding risk. Although randomized trial data on the use of such solutions in cardiac surgery were limited at the time of the 2001 meta-analysis, data have subsequently accumulated. This meta-analysis was designed to test, in light of all currently available randomized trial data, the null hypothesis that HES does not increase postoperative blood loss relative to albumin in patients undergoing CPB. Prespecified subgroup analyses were performed to evaluate potential differences in the effects on postoperative blood loss of the 3 most commonly used HES solutions, namely HES 450/0.7, HES 200/0.5, and HES 130/0.7. Possible differences in direct head-to-head randomized comparisons of these HES solutions were also assessed.

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Abbreviations and Acronyms

CI	= confidence interval
CPB	= cardiopulmonary bypass
FFP	= fresh-frozen plasma
HES	= hydroxyethyl starch
ICU	= intensive care unit
RBC	= red blood cell
RR	= relative risk

MATERIALS AND METHODS**Selection Criteria**

Randomized trials comparing HES 450/0.7, HES 200/0.5, or HES 130/0.4 with albumin in adult patients undergoing CPB were eligible. Head-to-head trials between any pairs of those 3 HES solutions could also be included. Postoperative blood loss data had to be available. No language or time period restrictions were applied. Trials were excluded if all patients in one group crossed over to receive the other test colloid during the study observation period, because such crossover would confound trial outcomes. Trials of Boldt and coworkers were excluded in light of public disclosures indicating scientific misconduct by those investigators (www.klilu.de/content/aktuelles___presse/pressearchiv/2010/untersuchungsbericht_der_kommission_fuer_die_pressekonferenz_am_29_november_2010/index_ges.html?raw=Boldt&ZMS_HIGHLIGHT=raw).

End Points

The primary end point was cumulative blood loss during the first 24 hours after CPB. Secondary end points were reoperation for bleeding and blood product transfusion during the first 24 postoperative hours. Additional supplementary end points were fluid balance, hemodynamics, time on ventilator, intensive care unit (ICU) stay, and mortality.

Search Methods

Published and unpublished trials were sought by computer searches of MEDLINE; Embase; the Cochrane Library; ClinicalTrials.gov; the US Food and Drug Administration and European Medicines Agency web sites; and abstract databases for major conferences in surgery, anesthesiology, and intensive care. Search terms included the following: hydroxyethyl starch, HES, hetastarch, pentastarch, tetrastarch, albumin, coronary artery bypass, bleeding, hemorrhage, blood transfusion, randomized controlled trial, and random allocation. Full-text Internet searches with the Google search engine were also performed. Investigators involved in fluid management for cardiac surgery and manufacturers of colloid products used in cardiac surgery were contacted as an aid in identifying eligible trials. Reference lists of primary research papers and review articles were consulted, and selected journals were searched by hand or their online tables of contents were examined. Data on file at US government agencies from eligible trials were requested under the Freedom of Information Act.

Data Extraction

Two investigators (R.J.N. and M.M.W.) independently determined trial eligibility and extracted data from the trial reports. Differences in interpretation were resolved through discussion. The investigators, patients, and methods in the trial reports were closely compared to avoid duplication. Extracted data consisted of the numbers of patients; age; indication for fluid administration; colloid regimen; type of HES solution; mean and SD of postoperative blood loss; reoperation for bleeding; units of red blood cells (RBCs), fresh-frozen plasma (FFP) and platelets transfused; cumulative fluid balance; heart rate; cardiac index; mean arterial pressure; central

venous pressure; pulmonary capillary wedge pressure; time on ventilator; ICU stay; and mortality. Queries were directed to the randomized trial investigators for further information as needed.

Statistical Analysis

The between-group standardized mean differences for postoperative blood loss and blood product transfusion were computed with 95% confidence intervals (CIs). The standardized mean difference, the customary effect size measure for continuous data in meta-analysis, expresses difference as a percentage of pooled standard deviation and is well-suited to postoperative blood loss and blood product transfusion data in cardiac surgery, which can vary many fold in scale between trials. In contrast to blood loss and blood product transfusion, other continuous variables did not display wide variability in scale between studies, and such data were analyzed without standardization as mean differences in the originally reported units of measurement. The relative risk (RR) of reoperation for bleeding and its 95% CI were also calculated. Heterogeneity was assessed by the Cochran Q test and the I^2 statistic. In the absence of significant heterogeneity, standardized mean difference and RR were combined across trials under a fixed effects model. Publication bias was evaluated by linear regression of standardized effect versus precision. Subgroup analyses were planned a priori to compare the effects of different HES solutions. The significance of subgroup differences was determined by test of interaction.

Role of Sponsor

The study sponsor played no role in the design of the study; in the collection, analysis, and interpretation of data; in manuscript preparation; or in the decision to submit for publication.

RESULTS**Included Trials**

Eighteen randomized trials with 970 total patients reported from 1982 to 2008 were included in the meta-analysis (Figure 1).²⁻²² The attributes of the included trials are summarized in Table 1. The median number of patients per trial was 48, with an interquartile range of 30 to 60. The indications for colloid use were volume expansion in 9 of the trials, pump priming in 5, and both in 4.

Three trials were reported in 2 publications each.^{12,13,19-22} One trial¹⁵ was reported in abstract form only, and full documentation of the trial design, data and statistical analysis was secured from the US Office for Human Research Protections. Another trial¹⁶ was unpublished, and the complete study report submitted by an HES manufacturer in support of a New Drug Application was obtained from the US Food and Drug Administration. Unpublished individual patient postoperative blood loss and blood product transfusion data for 3 included trials were furnished by the investigators on request.¹⁸⁻²²

HES 450/0.7 was compared with albumin in 9 trials and with HES 200/0.5 in 6. One of the 6 trials evaluating HES 200/0.5 also included a third study arm of 15 patients allocated to receive HES 130/0.4.^{21,22} No other included trials compared HES 130/0.4 with albumin, and consequently it was not possible to combine results quantitatively across trials of HES 130/0.4 versus albumin. Four trials, including the trial with the third arm receiving HES 130/0.4,^{21,22} compared HES 200/0.5 and HES 130/0.4 head to

FIGURE 1. Process of randomized trial selection. Appendices E1 and E2 provide reference citations for each report judged not eligible after screening and detailed examination, respectively, categorized by reason. HES, Hydroxyethyl starch.

head. Of those 4 trials, 3 were manufacturer-sponsored investigations with an equivalence hypothesis.^{14,16,17} No eligible head-to-head trials of HES 450/0.7 versus either HES 200/0.5 or HES 130/0.4 were identified.

Saline solution was the only HES solvent tested in all trials except 1. That trial compared HES 450/0.7 in balanced electrolyte with HES 450/0.7 in saline solution and albumin.¹⁵ Mean chest tube drainage during the first 24 postoperative hours for the group receiving HES 450/0.7 in balanced electrolyte (1355 ± 961 mL) did not differ significantly ($P = .85$) from that for recipients of HES 450/0.7 in saline solution (1388 ± 734 mL), and accordingly the data for those two HES 450/0.7 groups were pooled for the meta-analysis.

Bleeding

Among the included trials, mean postoperative blood loss in the albumin group ranged 4-fold, from 360 mL to 1373 mL (Figure 2). The corresponding range among HES recipients was 7-fold, from 217 mL to 1559 mL. Compared with albumin, HES increased postoperative bleeding by 33.3% of a pooled SD ($P < .001$), as shown in Figure 2 (A). There was no evidence of heterogeneity ($P = .40$) or publication bias ($P = .67$). For the 4 more contemporary trials reported

after 2000, the pooled increase in postoperative blood loss (49.7%; 95% CI, 23.0%–76.5%) among patients exposed to HES was greater than that in the 11 earlier trials from 1982 through 2000 (25.6%; 95% CI, 7.4%–43.8%); however, this difference was not statistically significant ($P = .14$).

The postoperative blood loss increases among patients receiving HES 450/0.7 (36.2%) and HES 200/0.5 (28.5%) did not differ significantly ($P = .62$). In 4 head-to-head randomized trials (Figure 2, B), there was no significant difference in postoperative blood loss ($P = .21$) between patients receiving HES 130/0.4 and those receiving HES 200/0.5.

Reoperation

Data on reoperations for bleeding were available from 15 of the 18 included trials. In 5 of the 15 trials with such data, no patients underwent reoperation for bleeding. The RR of reoperation for bleeding thus could be computed for 10 total trials.

As shown in Figure 3, A, the risk of reoperation for bleeding was more than doubled by HES (RR, 2.24; $P = .020$). Relative to albumin, the risk for HES 450/0.7 (RR, 2.13) did not differ significantly ($P = .87$) from that for HES 200/0.5 (RR, 2.38). In head-to-head comparisons of HES 200/0.5 relative to HES 130/0.4 (Figure 3, B), no difference in risk of reoperation for bleeding was detectable (RR, 0.77; $P = .62$).

Blood Products

Data were available for postoperative transfusion of RBCs in 14 of the 18 included trials, for transfusion of FFPs in 10 trials, and for transfusion of platelets in 9. Differences in trials with nonzero use of a particular blood product type are summarized in Table 2. Relative to albumin (Table 2), HES increased the transfusion of RBCs by 28.4% of a pooled SD ($P < .001$), of FFP by 30.6% ($P = .008$), and of platelets by 29.8% ($P = .027$). Between HES 450/0.7 and HES 200/0.5, no significant differences were evident for the increases in RBC ($P = .36$), FFP ($P = .47$), and platelet ($P = .74$) transfusions. In the 2 head-to-head trials with available blood product transfusion data (Table 2), no differences were found between HES 130/0.4 and HES 200/0.5 in transfusion of RBCs ($P = .24$), FFP ($P = .70$), or platelets ($P = .46$).

Fluid Balance

Data for cumulative fluid balance during the first 24 hours after surgery were available for 6 trials comparing HES with albumin. No significant differences were found (Table E1).

Hemodynamics

Tables E1 and E2 present analyses of hemodynamics at 24 hours after surgery for trials with such data reported. In patients receiving HES, heart rate was lower on average by 3.2 beats/min, cardiac index was lower by

TABLE 1. Included trials

Trial	n	Age (y, mean)	Indication	Surgery	Colloid regimen
Diehl et al, 1982 ²	60	57.4	VE	CABG	5% albumin vs 6% HES 450/0.7 in first 24 h
Moggio et al, 1983 ³	47	56.6	VE	35 CABG, 9 valve, 3 CABG and valve	5% albumin vs 6% HES 450/0.7 to postoperative cardiac index and PWP targets
Saunders et al, 1983 ⁴	20	60.7	PP	CABG	2.5% albumin vs 3% HES 450/0.7 asanguineous prime
Kirklin et al, 1984 ⁵	30	—	VE	CABG	5% albumin vs 6% HES 450/0.7 over 24 h to maintain 6–12 mm Hg left atrial pressure and $>2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ cardiac index
Gallagher et al, 1985 ⁶	10	53.9	VE	CABG	5% albumin vs 6% HES 450/0.7 to maintain 12–18 mm Hg postoperative PWP
Sade et al, 1985 ⁷	54	54	PP	CABG, valve, CABG and valve	0.9% albumin vs 1.0% HES 450/0.7 prime
London et al, 1989 ⁸	94	63	VE	71 primary and 3 repeat CABG, 12 primary and 4 repeat valve, 8 CABG and valve	5% albumin vs 10% HES 200/0.5 in first 24 h to maintain $\geq 2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ cardiac index and mean arterial pressure $\pm 10\%$ of baseline
London et al, 1992 ⁹	60	60	PP	56 CABG, 4 valve	3.8% albumin vs 3.8% HES 200/0.5 prime
Mastroianni et al, 1994 ¹⁰	34	60.1	VE	27 CABG, 2 valve	5% albumin vs 10% HES 200/0.5 in first 24 h to maintain $>2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ cardiac index, ≥ 100 mm Hg systolic blood pressure and ≤ 20 mm Hg PWP
Saxena et al, 1997 ¹¹	50	53	VE	CABG	5% albumin vs 6% HES 450/0.7 intraoperatively to replace $10 \text{ mL} \cdot \text{kg}^{-1}$ withdrawn blood
Tigchelaar et al, 1997 ^{12,13}	22	60.7	PP	CABG	4% albumin vs 2.5% HES 200/0.5 prime
Gallandat Huet et al, 2000 ¹⁴	59	62.3	VE and PP	CABG	Priming and perioperative volume expansion with 6% HES 130/0.4 vs 6% HES 200/0.5; 1000 mL of respective study HES solutions in prime (total prime volume unreported)
Bennett-Guerrero et al, 2001 ¹⁵	147	67.1	VE and PP	Primary CABG, valve, CABG and valve	Priming and intraoperative volume expansion with 5% albumin vs 6% HES 450/0.7 in normal saline solution vs 6% HES 450/0.7 in Ringer's lactate solution; 2.5%, 3% and 3% final prime concentrations, respectively
Frey, 2001 ¹⁶	61	62.1	VE and PP	Primary CABG	Priming and perioperative volume expansion with 6% HES 130/0.4 vs 6% HES 200/0.5; 500 mL of respective study HES solutions in prime (total prime volume unreported)
Kasper et al, 2000 ¹⁷	117	62.3	VE and PP	Elective primary CABG	Priming and perioperative volume expansion with 6% HES 130/0.4 vs 6% HES 200/0.5; 3% final prime concentration of study HES solution in both groups
Kuitunen et al, 2004 ¹⁸	30	58	PP	Elective primary CABG	Priming with $20 \text{ mL} \cdot \text{kg}^{-1}$ 4% albumin vs 6% HES 450/0.7, respectively, 3.4 and 4.9% final concentrations
Niemi et al, 2006 ^{19,20}	30	62.5	VE	29 CABG, 11 aortic valve, 5 mitral valve	$15 \text{ mL} \cdot \text{kg}^{-1}$ 4% albumin vs 6% HES 200/0.5 in ICU
Niemi et al, 2008 ^{21,22}	45	61	VE	14 CABG, 18 aortic valve, 5 mitral valve, 2 CABG and aortic valve, 6 composite	$15 \text{ mL} \cdot \text{kg}^{-1}$ 4% albumin vs 6% HES 130/0.4 vs 6% HES 200/0.5 in ICU

CABG, Coronary artery bypass grafting; HES, hydroxyethyl starch; ICU, intensive care unit; PP, pump priming; PWP, pulmonary wedge pressure; VE, volume expansion.

FIGURE 2. A and B, Postoperative blood loss. Error bars indicate 95% CI. Data points are scaled in proportion to meta-analytic weight. CI, 95% Confidence interval; HES, hydroxyethyl starch; SMD, standardized mean difference; SD, standard deviation.

0.17 L · min⁻¹ · m⁻², and central venous pressure was lower by 0.97 mm Hg. These differences were statistically significant. No corresponding differences were observed

in mean arterial pressure or pulmonary capillary wedge pressure. No hemodynamic differences could be demonstrated between HES 130/0.4 and HES 200/0.5.

FIGURE 3. A and B, Reoperations for bleeding. Graphic conventions are as given in Figure 2. CI, 95% Confidence interval; HES, hydroxyethyl starch.

Other Outcomes

Time on ventilator did not differ significantly between HES and albumin in 5 trials with data for this end point (Table E3). There was also no overall difference in ICU stay. Although there was evidence from a subgroup analysis that HES 200/0.5 significantly prolonged ICU stay relative to albumin by half a day, that result was derived from just 2 trials and hence should be viewed with caution. No differences in either time on ventilator or ICU stay were found between HES 130/0.4 and HES 200/0.5.

Mortality data were available from 11 of the 18 included trials. No deaths occurred in 6 of those 11 trials. In the remaining 5 trials with mortality data, a total of 12 patients died: 9 in trials comparing HES with albumin and 3 in head-to-head trials of HES 130/0.4 and HES 200/0.5.

With only 12 total events, no mortality differences were detectable (Table E3).

DISCUSSION

This meta-analysis confirms the finding of a 2001 meta-analysis¹ of increased blood loss after CPB among patients receiving HES compared with albumin. In contrast to the previous meta-analysis and to any individual randomized trial, this meta-analysis shows for the first time that the increase in blood loss is also accompanied by more frequent reoperation for bleeding and greater blood product transfusion. Additionally, the effects of HES did not differ detectably in relation to molecular weight and substitution. Although differences between HES solutions were not found in a number of individual trials, the statistical power to detect differences in those trials was limited. This

TABLE 2. Blood product transfusion

Colloids compared	Red blood cells	Fresh-frozen plasma	Platelets
HES 450/0.7 vs albumin	34.0% (13.8%–54.1%); 8 trials	25.6% (–0.6% to 51.8%); 4 trials	32.5% (1.7%–63.2%); 2 trials
HES 200/0.5 vs albumin	18.1% (–9.3% to 45.4%); 5 trials	44.6% (0.6%–88.5%); 3 trials	22.4% (–28.6% to 73.5%); 2 trials
Total	28.4% (12.2%–44.6%); 13 trials	30.6% (8.0%–53.1%); 7 trials	29.8% (3.4%–56.2%); 4 trials
<i>I</i> ² (95% confidence interval)	11% (0%–49%); <i>P</i> = .34	8% (0%–73%); <i>P</i> = .37	0% (0%–72%); <i>P</i> = .66
<i>P</i> for HES 450/0.7 vs HES 200/0.5	.36	.47	.74
HES 130/0.4 vs HES 200/0.5	24.9% (–16.8% to 66.6%); 2 trials	8.2% (–33.5% to 49.9%); 2 trials	15.8% (–25.8% to 57.5%); 2 trials
<i>I</i> ²	0%; <i>P</i> = .75	0%; <i>P</i> = .33	0%; <i>P</i> = .86

Data represent pooled standardized mean difference with 95% confidence interval except as marked. HES, Hydroxyethyl starch.

meta-analysis provides the first demonstration, as derived from the combined statistical power of 18 randomized trials, that increased bleeding, reoperation, and transfusion appear to be generic effects of HES solutions irrespective of molecular weight and substitution.

In the evaluation of HES, albumin is the most appropriate control fluid, because it is the colloid normally present in circulation and is free of adverse effects on coagulation. The safety of HES solutions, including their impact on bleeding, has often been claimed on the basis of comparisons with other artificial colloids. That approach is unsound, because the control artificial colloid may itself exert adverse effects, such as impairment of coagulation. From examination of head-to-head trials, this meta-analysis confirms the equivalence of HES 130/0.4 and HES 200/0.5; accordingly, the demonstrated adverse effects of HES 200/0.5 relative with albumin do not provide reassurance of a favorable safety profile for HES 130/0.4. In this context, there is a need for randomized trials directly comparing HES 130.0.4 with albumin in cardiac surgery. One such trial is currently ongoing ([ClinicalTrials.gov](#) identifier NCT01174719), and another has been announced ([ClinicalTrials.gov](#) identifier NCT01418521).

Among the trials included in this meta-analysis, patient enrollment criteria, fluid protocols, transfusion targets, and other aspects of clinical management strategy were not standardized. Nonetheless, differences in patient characteristics and treatment are unlikely to have confounded the conclusions of the meta-analysis for 2 reasons. First, the meta-analysis was restricted to randomized, controlled trials, and therefore extraneous factors other than type of colloid administered should not have generated any systematic bias. Second, if patient and treatment differences between trials were important determinants of outcome, then it should have been possible to detect heterogeneity; however, there was no evidence of heterogeneity in blood loss, reoperation for bleeding, or blood product transfusion. Another limitation of the meta-analysis was the inadequate available data comparing HES 130/0.4 directly with albumin.

To avoid potential sampling bias, a comprehensive systematic search strategy for eligible trials was implemented.

The strategy used multiple search methods and was designed to ensure, to the maximum extent possible, that the totality of relevant evidence was assembled for the meta-analysis. Prespecified trial eligibility criteria were adopted, and no ad hoc exclusions of trials were made whatsoever, to eliminate any selection bias. Finally, as a safeguard against possible publication bias, unpublished trial data were sought and secured.

Multiple mechanisms may explain the detrimental impact of HES on hemostasis after surgery with CPB, including depletion of circulating coagulation factors, impairment of platelet function, reduction in clot strength, and enhancement of fibrinolysis.^{22,23} In 2 of the randomized trials included in the meta-analysis,^{18,22} HES solutions were shown by thromboelastography to decrease maximum clot firmness in patients undergoing CPB. In 1 of those trials, the magnitude of the deleterious effect was closely similar between HES 130/0.4 and HES 200/0.5.²²

One major potential advantage of HES relative to albumin is its lower unit acquisition cost. On the other hand, in a retrospective case-control study of 288 patients, substitution of HES for albumin as the extracorporeal circuit priming fluid was associated with a dose-dependent increase in hemorrhage, and the added costs to treat hemorrhage were greater than the savings afforded by the lower acquisition cost of HES.²⁴ Another advantage of HES, a synthetic colloid, is more consistent supply. As a plasma-derived colloid, albumin is subject to periodic shortages. The in vitro colloid osmotic pressure of available 6% to 10% HES solutions is higher than that of the 4% to 5% albumin solutions investigated for volume expansion in surgery with CPB (Table 1). Additionally, in the majority of trials included in the meta-analysis dealing with pump priming, higher final concentrations of HES than albumin were used. Thus the HES solutions infused for volume expansion or incorporated in the extracorporeal circuit prime may have been capable of exerting higher oncotic forces in vivo that might potentially reduce interstitial fluid accumulation. Nevertheless, no significant difference was detected between HES and albumin in cumulative fluid balance during first 24 hours after surgery (Table E1).

Excessive bleeding and other HES-related complications may contribute to poorer survival after surgery with CPB. Exposure to artificial colloids, predominantly HES, was an independent risk factor for death in a retrospective hospital discharge database study of 548 deaths among 19,578 cardiac surgical patients, with an adjusted odds ratio of 1.25 (95% CI, 1.04–1.49).²⁵

CONCLUSIONS

HES was found to increase postoperative bleeding, reoperation for bleeding, and blood product transfusion after CPB in this meta-analysis of randomized trials. Differences in safety profile related to molecular weight and substitution were not apparent. These results support an evidence-based recommendation for the avoidance or cautious use of HES solutions in patients undergoing surgery with CPB.

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APPENDIX E1. Reports Judged Not Eligible After Screening

Each report judged not eligible is listed only once under a single reason, although multiple reasons may have applied. The category “Boldt and Colleagues Study” was reserved for reports from that group that would otherwise have been eligible except for public disclosures to date of scientific misconduct (www.klilu.de/content/aktuelles___presse/pressearchiv/2010/untersuchungsbericht_der_kommission_fuer_die_pressekonferenz_am_29_november_2010/index_gesamt.html?raw=Boldt&ZMS_HIGHLIGHT=raw), including fabrication of 3 cardiac surgical randomized trials comparing hydroxyethyl starch 130/0.4 with albumin (reference numbers 8–10 under “Boldt and Colleagues Study”). Reports from that group that would not have been otherwise eligible are listed under the applicable reasons for disqualification.

Ineligible Control Fluid

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Pediatric Cardiac Surgery

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Nonrandomized

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Boldt and Colleagues Study

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Animal Study

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Off-Pump Surgery

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APPENDIX E2. Reports Judged Not Eligible After Detailed Examination

No Blood Loss Data

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Nonrandomized

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Crossover to Hydroxyethyl Starch

- Choi YS, Shim JK, Hong SW, Kim JC, Kwak YL. Comparing the effects of 5% albumin and 6% hydroxyethyl starch 130/0.4 on coagulation and inflammatory response when used as priming solutions for cardiopulmonary bypass. *Minerva Anesthesiol*. 2010;76:584-91.

Ineligible Control Fluid

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TABLE E1. Fluid balance, heart rate, and cardiac index

Colloids compared	Fluid balance (mL)	Heart rate (beats/min)	Cardiac index (L · min ⁻¹ · m ⁻²)
HES 450/0.7 vs albumin	212 (−361 to 785); 2 trials	—*	−0.06 (−0.38 to 0.25); 3 trials
HES 200/0.5 vs albumin	−105 (−621 to 411); 4 trials	−2.3 (−5.5 to 0.8); 5 trials	−0.14 (−0.26 to −0.03); 5 trials
Total	37 (−347 to 420); 6 trials	−3.2 (−6.0 to −0.5); 6 trials	−0.17 (−0.24 to −0.11); 8 trials
I ² (95% confidence interval)	8% (0%–77%); P = .36	52% (0%–81%); P = .07	0% (0%–60%); P = .58
P for HES 450/0.7 vs HES 200/0.5	.42	.26	.49
HES 130/0.4 vs HES 200/0.5	—*	−2.7 (−7.6 to 2.3); 2 trials	0.00 (−0.07 to 0.07); 2 trials
I ²	—*	14%; P = .28	0%; P ≥ .999

Cumulative fluid balance during first 24 hours after surgery and heart rate and cardiac index at 24 hours after surgery. Mean difference computed as value for hydroxyethyl starch minus albumin and hydroxyethyl starch 130/0.4 minus hydroxyethyl starch 200/0.5. Data represent pooled mean difference with 95% confidence interval except as marked. *HES*, Hydroxyethyl starch. *Only 1 trial in this category with data for this end point.

TABLE E2. Mean arterial pressure, central venous pressure, and pulmonary capillary wedge pressure

Colloids compared	MAP (mm Hg)	CVP (mm Hg)	PCWP (mm Hg)
HES 450/0.7 vs albumin	—*	—*	—†
HES 200/0.5 vs albumin	−2.9 (−6.3 to 0.4); 4 trials	−0.97 (−1.82 to −0.12); 5 trials	−0.39 (−1.36 to 0.58); 5 trials
Total	−2.9 (−6.3 to 0.4); 4 trials	−0.97 (−1.82 to −0.12); 5 trials	−0.33 (−1.26 to 0.59); 6 trials
I ² (95% confidence interval)	0% (0%–83%); P = .43	0% (0%–28%); P = .88	0% (0%–64%); P = .62
P for HES 450/0.7 vs HES 200/0.5	—	—	.71
HES 130/0.4 vs HES 200/0.5	−1.4 (−6.6 to 3.8); 2 trials	−0.05 (−1.28 to 1.18); 2 trials	0.59 (−0.87 to 2.04); 2 trials
I ²	0%; P = .84	0%; P = .81	0%; P = .70

Values obtained 24 hours after surgery. Mean difference computed as value for hydroxyethyl starch minus albumin and hydroxyethyl starch 130/0.4 minus hydroxyethyl starch 200/0.5. Data represent pooled mean difference with 95% confidence interval except as marked. *CVP*, Central venous pressure; *HES*, hydroxyethyl starch; *MAP*, mean arterial pressure; *PCWP*, pulmonary capillary wedge pressure. *No trials in this category with data for this end point. †Only 1 trial in this category with data for pulmonary capillary wedge pressure.

TABLE E3. Time on ventilator, intensive care unit stay, and mortality

Colloids compared	Ventilator time (h)	ICU stay (d)	Mortality
HES 450/0.7 vs albumin	0.79 (−0.21 to 1.80); 3 trials	−0.04 (−0.17 to 0.09); 5 trials	—*
HES 200/0.5 vs albumin	0.86 (−2.74 to 4.46); 2 trials	0.51 (0.05–0.96); 2 trials	0.71 (0.16–3.12); 2 trials
Total	0.80 (−0.17 to 1.76); 5 trials	0.00 (−0.12 to 0.12); 7 trials	0.99 (0.27–3.57); 3 trials
I ² (95% confidence interval)	37% (0%–77%); P = .17	36% (0%–73%); P = .16	0% (0%–87%); P = .45
P for HES 450/0.7 vs HES 200/0.5	.97	.024	.43
HES 130/0.4 vs HES 200/0.5	−0.02 (−1.93 to 1.89); 2 trials	−0.08 (−0.32 to 0.16); 3 trials	0.59 (0.08–4.34); 2 trials
I ² (95% confidence interval)	0% (—); P = .95	0% (0%–76%); P = .65	0% (—); P = .60

Mean difference computed as value for hydroxyethyl starch minus albumin and hydroxyethyl starch 130/0.4 minus hydroxyethyl starch 200/0.5. Relative risk computed as value for hydroxyethyl starch divided by albumin and hydroxyethyl starch 130/0.4 divided by hydroxyethyl starch 200/0.5. Data represent pooled mean difference (pooled relative risk for mortality, not estimable for trials with 0 deaths in both groups) with 95% confidence interval except as marked. *HES*, Hydroxyethyl starch; *ICU*, intensive care unit. *Only 1 trial in this category with mortality data.