Hetastarch increases the risk of bleeding complications in patients after off-pump coronary bypass surgery: A randomized clinical trial

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Objective: Hetastarch is an artificial colloid widely used intraoperatively in fluid-replacement regimens. Previous studies have found that the intraoperative administration of hetastarch may increase the risk of postoperative bleeding in patients who undergo coronary artery bypass graft surgery with cardiopulmonary bypass. Previous published reports have not examined this risk in patients who underwent coronary artery bypass grafting without cardiopulmonary bypass.

Methods: In a randomized clinical trial, 156 patients undergoing off-pump coronary artery bypass grafting were assigned to receive either 1 liter of hetastarch or 1 liter of albumin as part of intraoperative volume replacement. Sample recruitment was halted in a review per protocol by the study's Data Safety Monitoring Committee. We assessed the rate of postoperative bleeding by monitoring the number of units of blood products transfused in the first 24 postoperative hours in the intensive care unit and the hourly chest tube drainage in the first 12 postoperative hours.

Results: Intraoperative administration of 1 liter of hetastarch was associated with statistically significant increases in 3 measures: transfusion requirements on postoperative day 1 (red blood cells, 1.14 vs 0.40 units, $P = .017$; fresh-frozen plasma, 0.57 vs 0.15, $P = .009$; platelets, 0.35 vs 0.10, $P = .013$); the overall likelihood of receiving transfusion on postoperative day 1 (46.2% vs 25.6%, $P = .012$); and the volume of chest tube drainage in the first 12 hours postoperatively (732.0 vs 563.6 mL, $P < .001$).

Conclusion: In patients undergoing off-pump coronary artery bypass, the intraoperative administration of hetastarch increases the postoperative transfusion requirement and the volume of blood drained postoperatively.

Postoperative bleeding is a major concern in coronary artery bypass graft (CABG) surgery. High-molecular-weight hydroxyethyl starch 6% (hetastarch) in a buffered electrolyte dextrose solution is an inexpensive artificial colloid now widely used as part of perioperative fluid-replacement regimens. There is now active debate¹⁻¹⁴ about whether the use of hetastarch for fluid replacement in CABG adds to the risk of postoperative bleeding.^{3,4,7,15} The debate has been fueled by inconsistent study results from individual studies.^{3,9-12} Analyses have noted inconsistencies among the studies and sample size and other methodological limitations of the individual previous experimental and nonexperimental studies.^{3,9,10,15-17} Variations in fluid replacement and operative protocol over the times when these source studies were

conducted limit their generalizability to the current practice environment.^{1,4,18-21} The question of the excess bleeding risk carried by hetastarch was settled for patients undergoing CABG by a case-control study¹ that found a dose-dependent association between postoperative bleeding and intraoperative use of hetastarch.

A high proportion, approximately 85% of the CABG procedures at our facility, and an increasing proportion of procedures performed at other facilities in the United States are conducted off pump (off-pump coronary artery bypass [OPCAB]).^{22,23} The "pump effect" on coagulation and other hemodynamic factors mean that findings regarding the risk of postoperative bleeding and other outcomes that have been obtained for CABG performed on pump may not apply to OPCAB performed off pump.^{10,24-26} As such, it is unclear whether a fluid now widely used for volume replacement in a common operation carries an increased risk of a major untoward outcome when that fluid is used in this operation.

We report the results of a randomized clinical trial designed to evaluate the effect of intraoperative administration of hetastarch on postoperative bleeding in patients who underwent OPCAB in an active cardiac surgery practice. Our study was designed to investigate the association of intraoperative hetastarch administration with the risk of postoperative bleeding in OPCAB. Our results will have important implications regarding the safety of hetastarch use in OPCAB as it is performed in regular clinical practice.^{1,5}

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Abbreviations and Acronyms

BMI	= body mass index
CABG	= coronary artery bypass graft
DSMC	= Data and Safety Monitoring Committee
FDR	= false discovery rate
ICU	= intensive care unit
INR	= international normalized ratio
OPCAB	= off-pump coronary artery bypass
POD	= postoperative day

METHODS AND MATERIALS**Eligibility**

We screened for eligibility all adult Kaiser Permanente members who were admitted to Alta Bates Summit Medical Center (Oakland, CA) between September 1, 2004, and July 27, 2005, for planned OPCAB. We obtained informed consent to participate preoperatively from screened patients who met the study eligibility criteria. We excluded pregnant patients and patients with a history of cardiac surgery, primary bleeding disorders, or end-stage renal disease from participation. This study design was reviewed and approved by institutional review boards of The Permanente Medical Group and the Alta Bates Summit Medical Center.

Statistical Power Analysis

We designed our power analysis for evaluation of the equivalence of a result in the study and control groups, defining a zone of equivalence for the statistical power analysis rather than basing our power analysis on the more usual clinically significant difference. We used volume of packed cells transfused within the first 24 hours postoperatively as the target outcome for the statistical power analysis. This outcome is routinely measured and reliably available from previous studies. We used the results published for one of the previous randomized trials⁸ as the basis for the specific hypotheses evaluated in our calculation of statistical power. Despite some design differences between our study and that conducted by Sade and colleagues,⁸ we based the statistical hypotheses on the results of their study because those results included the measurements of the amount of blood products transfused and the amount of chest tube drainage postoperatively in patients after CABG needed to conduct our power calculations. We investigated whether patients in whom hetastarch instead of albumin was used as a part of intraoperative colloid replacement received an equivalent amount of postoperative blood products in the first 24 hours postoperatively. We calculated statistical power using the confidence interval-based technique for normally distributed interval variables.²⁷ Sade and colleagues⁸ report that patients receiving albumin as priming fluid for CABG received 358 (standard deviation = 396) mL packed cells in the postoperative period ending 7:00 A.M. on postoperative day (POD) 1. We defined the range of equivalence as ± 100 mL and set the confidence interval at 95%. Power analysis indicated that a target sample size of 165 patients in each arm of the study (hetastarch and albumin) was needed to give our study a 90% statistical power to achieve a result that is statistically significant.

We used block randomization with 8 patients in each block to ensure that the maximum size of the difference between the study and the control groups would be 4 if the study were halted at any time before the full sample size had been recruited. We randomly assigned 156 consecutive patients to receive either 6% hetastarch or 5% albumin in the perioperative period (cf. discussion of sampling below). Randomization assignments were ordered by study number. The assignments were recorded on paper slips that were placed in opaque envelopes. Each envelope was coded by study number and sealed. The attending anesthesiologist opened the envelope linked to the patient's study number in the operating

room when the procedure was under way and administered 1 liter of hetastarch intraoperatively to patients assigned to the study group and 1 liter of albumin to patients assigned to the control group. All patients received the remaining standard operative regimen of crystalloids and blood products at the discretion of the anesthesiologist. After the first liter of colloid was administered, the patient received only albumin if more colloid was needed to meet additional requirements for fluid replacement. All patients were transferred postoperatively to the intensive care unit (ICU). The attending intensivists were blinded to the randomization. No hetastarch was administered postoperatively in the ICU.

Clinical Protocol

Operative procedures were performed by teams involving 11 anesthesiologists and 5 surgeons. The surgeons had between 3 and 8 years experience performing OPCAB.

Patients undergoing planned elective procedures were prepared following our hospital's standard protocol. The elective operations were scheduled at least 1 week after the last preoperative dose of clopidogrel bisulfate (Plavix; Sanofi-Aventis, Bridgewater, NJ). Plavix was reinitiated no earlier than 24 hours postoperatively at the physicians' discretion. No aspirin was administered during the final 24 preoperative hours. All patients were administered aspirin beginning 7 hours postoperatively. Anesthesiologists in our facility routinely use protamine to reverse the anticoagulant effects of heparin.

Postoperative fluid management, including blood product transfusion and replacement of crystalloids and albumin to maintain adequate blood pressure, cardiac index, and urine output, was performed at the discretion of the attending intensivist according to the clinical status of each patient. No attempt was made to implement rigorous thresholds for postoperative fluid replacement, that is, this study had no protocol for postoperative fluid replacement.

Information Collected

We prospectively collected the following demographic and preoperative data for all patients: age, gender, body mass index (BMI), urgency of surgery, serum albumin level, serum creatinine level, blood urea nitrogen level, hematocrit, platelet count, prothrombin time, and partial thromboplastin time, as well as preoperative administration of anticoagulants, antiplatelet medications, and thrombolytic agents. The scale we used to categorize the procedural urgency of the bypass differentiates elective procedures, urgent procedures performed in the same hospitalization as the cardiac catheterization, and urgent procedures performed as soon as possible after the cardiac catheterization. Perioperative data included the identity of the surgeon and anesthesiologist; patients' lowest body temperature and highest activated clotting time; and volume of crystalloids, colloids, and cell saver, and number of units of blood products administered. Postoperative measurements included the hourly chest tube drainage in the first 12 postoperative hours; the volume of crystalloid and albumin delivered and the number of units of blood products transfused, all for the first 24 hours postoperatively; and any reoperation of the chest to treat postoperative bleeding. We also recorded the duration of mechanical ventilation, duration of the stay in the ICU, total length of the hospital stay, and mortality in the ICU and during the total in-hospital stay.

Clinical Practices

With the exception of the choice of the fluid used for intraoperative volume replacement, all aspects of the care of patients in our study were left to the discretion of the attending physicians. Nonetheless, all of this care conformed to certain institutional practice patterns. Activated clotting time was used by the attending physicians to guide normalization during the procedure. Cell saver was used for all patients. Heparin was reversed by protamine at the end of all procedures. The determination of postoperative hemoglobin, initiation, and volume of postoperative red blood cell transfusion was left to the discretion of the attending intensivists involved in

providing the postoperative care. The intensivists and other clinicians providing postoperative care were kept blind to whether the patient had received hetastarch for intraoperative volume replacement. Only albumin was used for postoperative volume replacement. The initiation and volume of postoperative volume replacement were at the discretion of the attending intensivists.

Analytic Methods

We used the Fisher's exact test or Student *t* test for independent samples to conduct bivariate comparisons of study group measures with control group measures as appropriate given the nature of the measurement. We used analysis of covariance with general linear modeling and calculation of linear regression slopes to conduct multivariate comparisons of interval level-dependent measures between these groups while controlling for covariates. We used multiple logistic regression and calculation of slopes (logs of the odds ratio that can be treated within certain constraints as an estimate of the relative risk) to make similar comparisons for dependent variables measured at the nominal (specifically binary) level. For logistic regression, we used the omnibus test of model coefficients to summarize the statistical significance of the odds ratios modeled in the logistic regression equation as a whole. We used slopes and associated confidence intervals to model the associations for both the analysis of covariance and logistic regression. In addition to the analysis of statistical significance and modeling discussed above, the difference between the study and control groups was compared with the range of equivalence using confidence intervals constructed around marginal means that had been estimated to adjust for covariates. We conducted all analyses by intention to treat. After the exclusion of 4 subjects converted to on-pump procedures for medical reasons, all analyses of associations with the primary end point and key secondary outcomes were conducted on complete data from all randomized study participants (ie, the analysis of collected study data was identical to analysis by intention to treat). Virtually complete data collection on all subjects made it unnecessary to carry any observations forward or make any of the other adjustments that can be called for by intention-to-treat analyses). Analyses were conducted using Version 13.0.1 of SPSS for Windows (SPSS, Chicago, IL). We applied the false discovery rate (FDR) approach to analyses of the associations of multiple outcomes with the (randomly assigned) replacement fluid to control for the expected number of false-positive findings resulting from analyzing the association of common (ie, shared) predictors with multiple potential outcomes.²⁸ An explanation of the FDR procedure, the formula for adjusting target *P* values in accord with the FDR method, and the set of *P* values used in this study are shown in [Appendix 1](#). Particular statistical results are reported in the text only when those same results have not been reported in one of this article's results tables ([Tables 1–3](#)).

Target Outcomes

The study's primary outcome measures were the numbers of units of packed red blood cells, units of fresh-frozen plasma, and units of platelets transfused within the first 24 hours after surgery. These were chosen as primary end points because of known risks associated with transfusion of blood products. (The first 24 hours after surgery are also termed "POD 1" in the text below.) Secondary outcome measures included volume of chest tube drainage within the first 12 postoperative hours, frequency of reoperation for bleeding complications, duration of mechanical ventilation, length of stay in the ICU, length of total postoperative hospital stay, and total mortality rate. Chest-tube drainage was tracked over only the first 12 hours postoperatively because drainage in that period is most likely to reflect postoperative bleeding, whereas drainage occurring later may also reflect overall fluid overload and other processes leading to serous drainage.

Safety Monitoring Procedures

We aggressively monitored patient safety and any increase in adverse events associated with either or both of the trial arms. We established

a Data Safety Monitoring Committee. To ensure a clear cutoff point, we arbitrarily defined severe postoperative bleeding as chest tube drainage exceeding 1000 mL of blood in the first 12 postoperative hours. The study protocol called for the committee to meet after the first 15 patients reached this 1000-mL threshold value. We chose chest tube drainage to define the threshold for Data and Safety Monitoring Committee (DSMC) review because this drainage can be readily and unambiguously measured in a busy ICU, and because it is less subject to physician practice patterns than are the transfusion practices that are our study's primary outcome.²⁹ At that DSMC meeting, the committee was charged with evaluating the interim findings to determine whether either fluid carried an unacceptably increased risk of postoperative bleeding. Standard inferential tests for independent samples were used to compare relevant outcome rates for the hetastarch and albumin groups. Protocol called for repeat meetings of the DSMC after each 15 additional episodes of severe bleeding or earlier if investigators or the patients' referring clinicians raised questions about either of the arms carrying increased risk. Question was raised in our study after the first DSMC meeting when 2 additional subjects had drainage above the threshold level. Findings of analyses conducted for the DSMC indicated a statistically significant difference in postoperative drainage rates, and study recruitment was halted at that point. This safety monitoring process led to recruitment being halted before the full target sample size was reached. Despite this early end of enrollment before reaching the target sample size set by the statistical power analysis presented above, the study recruited an adequate sample size to demonstrate statistically significant associations with the primary end point and several of the secondary outcomes after using the FDR technique to adjust (ie, increase) the target significance levels for multiple tests against the same outcomes.²⁸

RESULTS

A total of 156 patients were enrolled in the study. Seventy-eight patients each were randomly assigned to the study (hetastarch) and control (albumin) groups. Four other patients were excluded after randomization because they were converted to on-pump surgery. Data collected from these 4 patients have been excluded from all data analyses. Conduct of the study did not deviate from the protocol or from any other aspects of the study design. Study recruitment was halted by the Data Safety Monitoring Committee, as noted above.

[Table 1](#) summarizes the demographic and clinical characteristics of all patients included in the study. There were no statistically significant differences between the study and control groups in any of the baseline characteristics.

The study and control groups were comparable with respect to all perioperative variables except the highest activated clotting time, which was higher in the control group (hetastarch 450.3 vs albumin 493.6, *P* = .022) and the volume of colloid administered, which was higher in the study group (hetastarch 1479.5 vs albumin 1192.3, *P* < .001) ([Table 2](#)). The median urgency of the operative procedure was 1 (elective) both in the sample as a whole and within the study and control groups. The difference in urgency between the study and control groups was not statistically significant (median test χ^2 with Yates' continuity correction = 0.646, *df* = 1, *P* = .42, not significant). Care was provided by 11 anesthesiologists and 5 surgeons. No statistically significant association was observed between the randomization

TABLE 1. Baseline characteristics of patients receiving hetastarch (study group) or albumin (control group)

	Hetastarch mean (SD) n*	Albumin mean (SD) n*	Statistical test test result (df)	P value
Age, y	64.1 (9.8) n = 78	64.4 (9.0) n = 78	Student <i>t</i> test = 0.229 (df = 154)	.82, NS
Sex, male	82.1% n = 78	70.5% n = 78	Fisher's exact test	.13, NS
Body mass index	27.5 (4.8) n = 78	28.9 (5.3) n = 78	Student <i>t</i> test = 1.65 (df = 154)	.10, NS
Serum albumin level (g/dL)	3.75 (0.39) n = 59	3.69 (0.47) n = 63	Student <i>t</i> test = -0.83 (df = 120)	.41, NS
Serum creatinine level (mg/dL)	1.11 (0.31) n = 78	1.10 (0.33) n = 78	Student <i>t</i> test = -0.23 (df = 154)	.82, NS
Serum urea nitrogen level (mg/dL)	19.76 (8.61) n = 78	18.32 (6.91) n = 78	Student <i>t</i> test = -1.15 (df = 154)	.25, NS
Hematocrit (%)	40.26 (4.18) n = 78	40.22 (4.39) n = 78	Student <i>t</i> test = -0.052 (df = 154)	.96, NS
Platelet count ($\times 10^3/\mu\text{L}$)	228.96 (58.30) n = 78	230.74 (66.07) n = 78	Student <i>t</i> test = 0.18 (df = 154)	.86, NS
Prothrombin time (INR)	1.47 (2.12) n = 78	1.07 (0.10) n = 78	Student <i>t</i> test = -1.65 (df = 77.35)	.10, NS
Activated partial thromboplastin time (s)	38.56 (36.11) n = 78	33.02 (15.73) n = 78	Student <i>t</i> test = -1.24 (df = 105.21)	.22, NS
Preoperative use of intravenous heparin	24.4% n = 78	30.8% n = 78	Fisher's exact test	.47, NS
Preoperative use of low-molecular-weight heparin	15.4% n = 78	14.1% n = 78	Fisher's exact test	1.00, NS
Preoperative use of glycoprotein IIb/IIIa inhibitors	10.3% n = 78	12.8% n = 78	Fisher's exact test	.80, NS
Preoperative use of platelet inhibitors	3.8% n = 78	11.5% n = 78	Fisher's exact test	.13, NS
Preoperative use of warfarin	1.3% n = 78	1.3% n = 78	Fisher's exact test	1.00, NS
Preoperative use of thrombolytic agents	3.8% n = 78	1.3% n = 78	Fisher's exact test	.62, NS

NS, Not significant; INR, international normalized ratio; SD, standard deviation. *n = 78 in all cells unless otherwise noted.

assignment and the identity of the participating surgeon or anesthesiologist.

Primary Outcomes

Bivariate analyses showed that the study group had increased transfusion requirements for all blood products on POD 1: red blood cells (1.14 vs 0.40 units, $P = .018$), fresh-frozen plasma (0.57 vs 0.15 units, $P = .009$), and platelets (0.35 vs 0.10 Super-packs, $P = .014$), all statistically significant (full statistical results readily available on request). The study group also had a higher overall likelihood of receiving a transfusion on POD 1 (46.2% vs 25.6%, $P = .012$). The results of multivariate analyses examining the association of hetastarch use with outcomes on POD 1, while controlling for age and BMI, are presented in Table 3. The volume of red blood cells is associated with hetastarch ($P = .006$) and age ($P = .0002$). The volume of colloid is associated with hetastarch ($P < .0001$). The number of packs of platelets transfused is associated with hetastarch ($P = .014$) and age ($P = .0023$). The number of units

of fresh-frozen plasma transfused is associated with hetastarch ($P = .009$) and age ($P = .001$). The receipt of any blood product on POD 1 is associated with hetastarch ($P = .008$) and age ($P = 2 \times 10^{-5}$). The ICU length of stay is associated only with age ($P = .0006$). The total hospital length of stay is associated with age ($P < 5 \times 10^{-6}$) and BMI ($P = .042$). Of these associations, only the statistical significance of the association of the total hospital length of length of stay with BMI fails to satisfy the FDR threshold. None of the predictors had any statistically significant associations with cryoprecipitate use on POD 1, repeat operations to control bleeding, or hours of mechanical ventilation. No study subject died before hospital discharge. The adjusted intergroup differences on the primary and important secondary outcome measures all exceeded the equivalence threshold.

Secondary Outcomes

Compared with controls (average = 563.6 mL), the study group (average 728.7 mL) had statistically significantly

TABLE 2. Intraoperative and baseline data for patients receiving hetastarch (study group) or albumin (control group)

	Hetastarch mean (SD)*	Albumin mean (SD)*	Statistical test, test result, df	P value
Lowest body temperature ($^{\circ}\text{C}$)	35.6 (0.58)	35.6 (0.54)	Student <i>t</i> test = -0.93, df = 154	.35, NS
Highest activated clotting time (sec)	450.3 (85.48)	493.6 (141.00)	Student <i>t</i> test = 2.32, df = 126.86	.022
Volume of crystalloid (mL)	2976.3 (1358.28)	3030.1 (988.06)	Student <i>t</i> test = 0.28, df = 140.66	.78, NS
Volume of colloid (mL)	1479.5 (545.85)	1192.3 (303.99)	Student <i>t</i> test = -4.06, df = 120.58	<.001
Cell saver (mL)	489.1 (403.25)	471.3 (331.66)	Student <i>t</i> test = -0.30, df = 154	.76, NS
Red blood cells (No. of units)	0.44 (0.85)	0.38 (0.79)	Student <i>t</i> test = -0.39, df = 154	.70, NS
Platelets (No. of 6-packs)	0.09 (0.37)	0.06 (0.37)	Student <i>t</i> test = -0.43, df = 154	.67, NS
Fresh-frozen plasma (No. of units)	0.15 (0.70)	0.13 (0.59)	Student <i>t</i> test = -0.25, df = 154	.81, NS
Cryoprecipitate (No. of units)	0.00 (0.00)	0.13 (1.13)	Student <i>t</i> test = 1.00, df = 77.00	.32, NS
No. of grafts	3.55 (1.04) n = 78	3.45 (0.91) n = 77	Student <i>t</i> test = -0.61, df = 153	.54, NS
Urgency of the procedure (median)	1	1	Median test χ^2 with Yates' continuity correction = 0.65, df = 1	.42, NS

NS, Not significant; SD, standard deviation. *n = 78 in all cells unless otherwise noted.

TABLE 3. Outcome data for patients receiving hetastarch (study group) or albumin (control group)

Outcome	Hetastarch mean* (SD) n	Albumin mean* (SD) n	Statistical Test	Slope (95% CI) <i>P</i> value				
				Hetastarch‡	Age	BMI	Intercept	Corrected model
Mean No. of units of red blood cells transfused on POD 1	1.13 (2.52) 78	0.40 (0.89) 78	Univariate ANCOVA	(−0.08) (−1.39) to (−0.23) <i>P</i> = .006	0.059 0.03–0.09 <i>P</i> = .0002	0.047, (−0.01) to 0.11 <i>P</i> = .11, NS	(−3.96) (−6.82) to (−1.09) <i>P</i> = .002	F = 6.928 <i>df</i> = 3152 <i>P</i> = .0002
Mean chest tube drainage in first 12 h	728.7 (323.5) 78	563.6 (197.9) 78	Univariate ANCOVA	−148.28 (−228.96) to (−67.60) 0.0004	5.330 0.97–9.69 0.0169	(−13.955) (−22.10) to (−5.81) .0009	771.624 374.55–1168.70 .0002	F = 12.765 <i>df</i> = 3152 <i>P</i> < 2 × 10 ^{−7}
Mean volume of colloid (mL)	1479.5 (545.8) 78	1192.3 (304.0) 78	Univariate ANCOVA	−286.35 (−427.76) to (−144.94) <i>P</i> < .0001	4.2 (−3.4) to 11.9 <i>P</i> = .27, NS	(−1.7) (−16.0) to 12.6 <i>P</i> = .81, NS	1255.0 559.0–1951.0 <i>P</i> < .0005	F = 5.95 <i>df</i> = 3152 <i>P</i> = .0007
Mean No. of superpacks (12-packs) of platelets transfused on POD 1	0.35 (0.77) 78	0.13 (0.38) 78	Univariate ANCOVA	−(0.23) (−0.41) to (−0.041) <i>P</i> = .014	0.016 0.006–0.026 0.0025	−0.016 (−0.035) to 0.003 0.10, NS	(−0.219) (−1.14) to 0.70 0.64, NS	F = 7.27 <i>df</i> = 3152 0.0001
Mean No. of units of fresh-frozen plasma transfused on POD 1	0.56 (1.24) 78	0.15 (0.56) 78	Univariate ANCOVA	(−0.39) (−0.68) to (−0.10) 0.009	0.031 0.016–0.047 0.0001	(−0.025) (−0.054) to 0.005 0.10, NS	(−0.762) (−2.19) to 0.67 0.29, NS	F = 9.98 <i>df</i> = 3152 <i>P</i> < 5 × 10 ^{−6}
Mean No. of units of cryoprecipitate transfused on POD 1	0.38 (2.52) 78	0.13 (1.13) 78	Univariate ANCOVA	(−0.27) (−0.90) to 0.35 0.39, NS	.018 (−0.02) to 0.05 0.29, NS	.01 (−0.05) to 0.07 0.77, NS	(−1.04) (−4.12) to 2.04 0.51, NS	F = 0.60 <i>df</i> = 3152 <i>P</i> = .62, NS
Percentage of patients who received blood products on POD 1	46.2% 78	25.6% 78	Logistic regression	2.78‡ 1.30–5.94 0.008	1.10‡ 1.06–1.15 0.00002	0.94‡ 0.86–1.02 0.94, NS	0.004 <i>P</i> < .006	$\chi^2_{2,d}$ = 36.45 <i>df</i> = 3 <i>P</i> = 6 × 10 ^{−8}
Percentage of patients who were returned to the operating suite for bleeding	3.8% 78	1.3% 78	Logistic regression	2.98 0.30–29.96 0.35, NS	1.08 0.96–1.21 0.19, NS	0.94 0.75–1.19 0.62, NS	0.0 0.17, NS	χ^2 = 3.49 <i>df</i> = 3 <i>P</i> = .32, NS
Mechanical ventilation (h)	26.3 (126.54) 78	13.8 (29.47) 78	Univariate ANCOVA	(−10.80) (−40.08) to 18.48 0.47, NS	(−1.31) (−2.89) to 0.27 0.10, NS	(−0.87) (−3.83) to 2.09 0.65, NS	134.25 (−9.87) to 278.37 0.07, NS	F = 1.15 <i>df</i> = 3152 <i>P</i> = .33, NS
ICU stay (d)	1.64 (0.98) 78	1.96 (2.10) 78	Univariate ANCOVA	0.28 (−0.23) to 0.79 0.28, NS	0.05 0.02–0.08 0.0006	.49 (−0.03) to 0.07 0.49, NS	(−2.00) (−4.49) to 0.50 0.12, NS	F = 4.69 <i>df</i> = 3152 <i>P</i> < .004
Hospital stay (d)	7.69 (2.57) 78	8.53 (4.27) 78	Univariate ANCOVA	(−0.10) (−0.79) to 0.59 0.77, NS	.09 0.05–0.13 <i>P</i> < 5 × 10 ^{−6}	.07 0.003–0.142 0.042	(−1.53) (−4.93) to 1.86 0.37, NS	F = 8.01 <i>df</i> = 3152 <i>P</i> < 6 × 10 ^{−5}
No. of patients who died during hospital stay	0	0	N/A	0	0	0	N/A	N/A

ANOVA, Analysis of variance; ANCOVA, analysis of covariance; ICU, intensive care unit; BMI, body mass index; SD, standard deviation; NS, not significant; N/A, not available; POD 1, postoperative day 1 (defined as the first 24 hours in the ICU after surgery or the total time spent in the ICU, whichever came first). Direct percentages, means, and standard deviations not adjusted for covariates. *Estimated marginal averages adjusted for covariates. †Estimate of odds ratio and 95% confidence interval for that estimate of the odds ratio. ‡Statistical significance was tested against target *P* values adjusted for multiple comparisons using the FDR developed by Benjamini in 1995 as the Bonferroni-type control. All associations with hetastarch that are statistically significant by the above multivariate analyses remain so by comparison with the FDR target values. The Benjamini formula and target *P* values are shown in Appendix 1. ^dOmnibus test of model coefficients. ‡n = 78 in all cells unless otherwise noted.

higher total drainage from chest tubes within the first 12 postoperative hours ($P < .0002$ by bivariate analysis). We used analysis of covariance to control for the influence of age and BMI. Analysis of covariance found the associations of total 12-hour chest tube drainage with hetastarch ($P < .0004$), BMI ($P = .0009$), and age ($P < .017$) all statistically significant (Table 3). All of these probabilities are below the target thresholds set by FDR analysis and remain statistically significant after controlling for multiple comparisons for each outcome.

During the intraoperative period, the study group received more colloid (average 1479.5 mL) than those who were administered albumin (average 1192.3 mL, $P < .001$). The average activated clotting time during this period was 450.3 seconds in the study group and 493.6 seconds in the control group, a statistically significant difference ($P = .022$). No other intergroup differences of measurements made during the operative period were statistically significant or demonstrated a trend (Table 2).

We examined the relation between risk of bleeding and age, serum albumin level, creatinine level, and BMI (Table 3). We found that increased age is associated with increased volumes of red blood cells ($P = .0002$), fresh-frozen plasma ($P = .0001$), and platelets transfused ($P = .0025$). Increased BMI is not a statistically significant risk factor for any of the bleeding outcomes. On consideration of use outcomes, higher age is associated with prolonged stay in the ICU ($P = .0006$) and hospital ($P < 5 \times 10^{-6}$). Age also demonstrates a trend toward increased duration of mechanical ventilation ($P = .10$, NS). The association of BMI with total length of stay is statistically significant ($P = .042$), but the results of the statistical significance test for that association do not pass the FDR threshold. Multivariate analysis does not find any of the associations between serum albumin level and any of the targeted outcomes to be statistically significant. As such, serum albumin level has been excluded from the analyses described here.

DISCUSSION

Hetastarch is an inexpensive plasma expander. It is routinely used in many medical facilities for intraoperative volume replacement in patients undergoing cardiac surgery. Previous studies have found the intraoperative use of hetastarch for volume replacement to be associated with increased postoperative bleeding after on-pump cardiac surgery (ie, CABG).^{1-4,7,9,10,11,15} Approximately 85% of the cardiac surgery in our facility follows a different strategy and is now performed off pump (ie, OPCAB).^{22,23} Our randomized trial investigated the equivalence of the risk of postoperative bleeding between intraoperatively administered albumin and hetastarch in patients undergoing OPCAB. To our knowledge, our study is the first randomized clinical trial designed to have adequate statistical power to examine the risks associated with intra-

operative use of hetastarch for fluid replacement in patients undergoing OPCAB as it is performed in regular clinical practice. As such, we established and adhered to protocols for selecting patients to whom hetastarch would be administered and the volume that would be administered. The project data set aggregated key clinical data. Our conduct of the study in a busy community cardiac operating room without functioning comprehensive computerized clinical information at the time we conducted the study limits the amount of information we collected for the project dataset. Additional information (eg, hemodynamic data) were hand-abstracted prospectively from the routine clinical records.

Previous studies examining volume replacement in OPCAB have not led to consensus regarding its safety. The strength of these previous studies may have been limited in part by aspects of their design. The sample sizes in the previous published randomized trials have ranged from 22 to 94.^{2,8,9} These negative randomized trials may well have been underpowered because of these small sample sizes: The largest sample size in any of these randomized trials is less than 30% of the target sample size indicated by the statistical power analyses we conducted for our study (vide supra) and less than the overall ($n = 200$) sample size calculated in a previous review¹⁰ for studies to have 90% power at P less than .05 to detect a 10% increase in blood loss above that reported by Boldt and colleagues.⁹

Our multivariate analyses of associations with the primary and secondary outcomes have statistically significant results. Before these results, some may have assumed that the increased bleeding associated with hetastarch administration was related to pump use during cardiopulmonary bypass use rather than to hetastarch.^{10,24-26} Our results indicate rather that hetastarch carries a risk of increased postoperative bleeding that is statistically and clinically significant in patients undergoing OPCAB, coronary artery bypass in which the operation is performed without cardiopulmonary bypass. The statistical strength of each principal comparison between the hetastarch and the albumin groups is robust. The adjusted estimates and confidence intervals around the intergroup differences for the primary outcomes dependably fall outside the zone of equivalence. These results remain statistically significant after all valid adjustments for multiple comparisons.

We also examined whether preoperative thrombolysis or international normalized ratio (INR) affected the volume of postoperative bleeding. The volume of postoperative bleeding is not associated with INR use ($P = .93$, NS). The association with preoperative thrombolysis demonstrates a trend that only reaches borderline statistical significance if INR is excluded from the analysis (figures readily available on request). Its inclusion has no effect on which associations reach or fail to reach statistical significance. As

such, we have excluded both INR and preoperative thrombolysis from the multivariate analyses (Table 3). No members of the study or control groups were returned to the operating room for control of postoperative bleeding. Return to the operating room was at the discretion of the attending intensivists and surgeons, as with other aspects of postoperative care. In our facility, the criteria considered in the decision to return a patient to the operating room for bleeding control post-CABG or OPCAB are the rate of bleeding, the degree of hemodynamic instability, and the presence or absence of correctable factors such as hypothermia and coagulopathy.

The increased risk of postoperative bleeding associated with the use of intraoperative hetastarch raises important questions about the safety of its use in these patients. Our study was not designed to investigate the mechanism underlying the increased risk of postoperative bleeding carried by hetastarch. Authors have hypothesized that the increased risk could result from 1 or more of several mechanisms: hetastarch precipitating some coagulation factors, making them unavailable to the coagulation cascade; hetastarch forming a complex with factor VIII and fibrinogen; the fibri-noplastic effect; and hetastarch coating the platelet surface, causing platelet damage.^{10,17}

Please note in this context, however, that albumin is more expensive than hetastarch and has been found to carry its own risks.^{16,29} Even the need for colloid administration during and after heart surgery is a subject of discussion. Further clinical studies may need to be conducted to clarify whether volume replacement needs in similar future patients would be best served by administering only crystalloid.

Study Limitations

Our study has several limitations. It was conducted in a single facility that was the only study location. A multicentered study might help to strengthen our findings regarding hetastarch safety by evaluating whether our findings resulted from idiosyncrasies of our patient population or surgical practices. Further, all patients in our study group were administered 1 liter of hetastarch in the operating room. No hetastarch was infused in the postoperative period to members of the study group. No hetastarch was administered to control group patients at any time during the study. As such, our project data do not allow evaluation of any threshold effect or dose-response association between the volume of hetastarch administered and the occurrence or volume of postoperative bleeding. Future studies will be needed to investigate the questions of a possible threshold effect or dose response between the volume of hetastarch administered and the amount of postoperative bleeding. Our study's protocol specified only if hetastarch was to be administered, the volume of hetastarch to be administered, and certain key preoperative and postoperative clin-

ical measurements. Other aspects of the preoperative and postoperative care and data collection were left to the attending clinicians' discretion. Study group patients were administered more colloid in the operating room than were control group patients (a difference of ~287 mL, $P < .001$). We hypothesize that this difference may have been linked to increased immediate hemodynamic instability in that group. Because the anesthesiologists administering the fluid were not blind to the volume replacement fluid that had been used, this greater volume may have resulted from prophylactic steps taken by the anesthesiologists. Future studies can explore whether hetastarch use is linked to increased immediate hemodynamic instability.

We took care to make this study methodologically sound and robust, using the FDR technique to address the risk of false conclusions associated with multiple comparisons²⁸ and a DSMC to monitor this intervention's risk. The results reported here as statistically significant were reached after the early termination of recruitment recommended by the DSMC had resulted in its sample size being well below that called for in study planning by our statistical power analysis. All important results remain statistically significant after application of the FDR adjustment of cut-points. Postoperative transfusion and fluid replacement were managed by the staff intensivists who were blinded to the intraoperative fluid administration. Transfusion was administered not per protocol but in accord with the intensivists' clinical judgment. That judgment in turn was based on multiple factors including but not limited to the volume of chest tube drainage and hematocrit. As such, the postoperative transfusion rates are an imperfect index of postoperative bleeding in this trial. This imperfection of transfusion rates as an index of postoperative bleeding has been found to be the case in other previous investigations.³⁰ The consistency of our multiple measures of postoperative fluid loss and replacement leaves us confident that these results indicate that hetastarch use is associated with clinically and statistically significant increased postoperative bleeding.

CONCLUSIONS

Intraoperative administration of hetastarch carries an increased risk of postoperative bleeding after OPCAB. Our study found hetastarch to have clinically and statistically significant associations with increases in the amount transfused and the volume of postoperative bleeding in patients undergoing OPCAB. Differences in key outcomes between those infused with hetastarch and those infused with albumin fell outside the zone of equivalence. These differences also passed the FDR statistical threshold designed to guard against the risk of false-positive conclusions resulting from performing multiple comparisons. Previous studies have found hetastarch use to be associated with increased risk

of postoperative bleeding after CABG procedures conducted on pump.¹ Our study extends those findings to off-pump OPCAB procedures. Our findings with respect to the study's primary outcomes are strong and definite. Our results reported here combined with those earlier results thus raise serious questions about the advisability of using hetastarch as the default volume expander in CABG. Our study was not statistically powered for analysis of the association between intraoperative fluids administered and other outcomes, such as length of mechanical ventilation, length of ICU and hospital stay, and mortality rates. Our findings with regard to these secondary outcomes should therefore be regarded as exploratory. Our findings with respect to the study's primary outcomes are stronger and more definite.

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Appendix 1

Procedure to control the FDR resulting from multiple comparisons.²⁹

The FDR approach adjusts the target significance levels for each analysis in a series of analyses of the associations of a set of shared predictors with a group of specified outcomes so that the target significance level for the analysis of the association of the predictors with each of these spec-

ified outcomes can be treated as equivalent to the standard significance level of $P < .05$. We used this technique to set target significance levels for the associations of each of the 3 predictors (ie, hetastarch, BMI, and age) with each of the specified outcomes (eg, units of red blood cells transfused in the first 24 hours postoperatively, chest tube drainage in the first 12 hours postoperatively, and so on).

Let $H_1, H_2, \dots, H_m$, be the hypotheses sharing certain characteristics (eg, predictors). Let $p_{(1)}, p_{(2)}, \dots, p_{(m)}$ be the corresponding P values. Let $p_{(1)} \leq p_{(2)} \leq \dots \leq p_{(m)}$ be the ordered P values. Denote by $H_{(i)}$ the null hypothesis corresponding to $P_{(i)}$. Then define the following Bonferroni-type multiple testing procedure:

let k be the largest i for which $P_{(i)} \leq (i/m)q^*$
then reject all $H_{(i)}$ $i = 1, 2, \dots, k$.

The target P threshold values generated by this procedure for results equivalent to $P < .05$ by comparison for the current study are as follows:

Comparison	Target
1	.005
2	.009
3	.014
4	.018
5	.023
6	.027
7	.032
8	.036
9	.041
10	.045
11	.050