Hemodilution and surgical hemostasis contribute significantly to transfusion requirements in patients undergoing coronary artery bypass

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Extra illustrations are available online.

Objective: We sought to determine the incidence of and risk factors for the development of low intraoperative hematocrit levels and of excessive postoperative bleeding in patients undergoing coronary artery bypass grafting, whether the risk factors are the same, and their effect on blood product transfusions.

Methods: We performed a prospective cohort study of 613 adult patients who underwent coronary artery bypass grafting in 3 tertiary, university-affiliated hospitals during the period from October 1, 2000, to March 31, 2001.

Results: Low intraoperative hematocrit levels (<19%) were found in 131 (24%) patients who had operations performed with extracorporeal circulation compared with in 3 (4%) patients with operations performed off pump. In multivariate analysis this was associated with older age, female sex, lower preoperative hemoglobin levels, lower body surface area, longer duration on bypass, and use of higher total volumes with more hydroxyethyl starch in the circuit. Low intraoperative hematocrit levels did not predict excessive postoperative hemorrhage (>1 L of mediastinal drainage in the first 12 hours). This occurred in 26% (n = 140) of patients undergoing on-pump operations and in 25% of patients undergoing off-pump operations and in multivariate analysis was associated with male sex, longer pump times, not receiving aprotinin, and operations performed by certain surgeons but not with total circuit or hydroxyethyl starch volume.

Conclusions: We observed that the risk factors for the development of a low intraoperative hematocrit level and excessive postoperative bleeding differed. Our results suggest that decreasing these outcomes in patients undergoing cardiac surgery requires a comprehensive approach, including limiting hemodilution, particularly in female subjects with lower preoperative hemoglobin levels, and careful attention to surgical hemostasis.

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Patients who undergo cardiac surgery commonly receive blood product transfusions, but there are substantial and unexplained differences in rates in different institutions.^{1,2} Consensus recommendations are to consider intraoperative transfusion of packed cells if the hematocrit level decreases to less than 19% intraoperatively.^{3,4} Drainage in excess of 1 L postoperatively is associated with accelerated transfusion of blood products in the order of greater than 5 units.^{2,5} Both excessive bleeding and low hematocrit levels are common and associated with worse outcomes,⁶⁻⁸ yet these have not been well characterized.^{2,6} Because of the assumption that risk factors for perioperative blood product transfusions^{3,9,10} and for bleeding are the same, preventive strategies have focused on agents promoting or limiting preoperative use of agents that impair hemostasis.¹¹⁻¹⁴ However, intraoperative anemia might be related to hemodilution, but this has received scant attention.¹⁵⁻¹⁷ It is also unclear whether the substantial differences in blood product

use related to cardiac surgery¹ stem from different transfusion practices or protocols, intraoperative antifibrinolytic use, surgical technique, or differences in patient populations.

After observing differences in practices in cardiac surgery in the 3 affiliated hospitals at our university, we prospectively evaluated the occurrence and risk factors for excessive postoperative hemorrhage and low intraoperative hematocrit values.

Methods

Setting and Study Population

The study was conducted in 3 general, tertiary, university-affiliated adult hospitals. In hospital A approximately 800 cardiac surgery procedures are performed annually by 4 surgeons, whereas in hospitals B and C approximately 500 such procedures are performed annually, primarily by 2 surgeons at each site; one surgeon operated in both hospitals B and C. In hospital A, a total volume of 2000 mL was used initially in the extracorporeal circuit in all patients, 750 mL of which was hydroxyethyl starch (HES), whereas in hospitals B and C, the total volume was 1400 mL, of which 500 mL was HES.

None of the hospitals had written transfusion protocols. As antifibrinolytic agents, aprotinin was routinely used in hospital A, whereas tranexamic acid was routinely used in the other 2 hospitals. During the time of the study, aprotinin was temporarily unavailable from the manufacturer, and as a result, 46 patients in hospital A underwent cardiac surgery without any antifibrinolytic agent. All patients were admitted to the intensive care unit (ICU) postoperatively, and retransfusion of shed mediastinal blood was practiced at all sites.

Data were collected prospectively on 613 consecutive patients who had undergone coronary artery bypass graft (CABG) procedures only without any valvular operations from October 1, 2000, to March 31, 2001, in hospitals B and C and from December 1, 2000 to March 31, 2001, in hospital A. A total of 545 procedures were performed on pump, and 68 were performed off pump across the 3 sites. The study was approved by the research ethics committees of the participating institutions.

Data Collection

The following data were collected from standardized data collection sheets.

Preoperative characteristics included age, sex, body surface area, Parsonnet score,¹⁸ history of prior cardiac surgery, premorbid diagnoses (eg, diabetes mellitus, hypertension, renal failure, coagulation disorders, and left ventricular dysfunction), and whether surgical intervention was required within 6 hours (ie, an emergency procedure). We also recorded preoperative use of drugs that impair hemostasis, such as aspirin, clopidogrel, heparin, or warfarin, as well as preoperative hemoglobin level, international normalized ratio, partial thromboplastin time, and platelet count.

Intraoperative factors included identity of the primary surgeon, antifibrinolytic agent used, time on extracorporeal circulation, lowest intraoperative hematocrit level recorded, type and number of blood products transfused intraoperatively, highest recorded acti-

vated clotting time, and total number of grafts, including whether arterial or vein grafts were used.

Postoperative factors included hemoglobin and coagulation parameters, need for exploratory reoperation, mortality, length of stay in the ICU and length of hospitalization, mediastinal drainage in the first 12 hours, and number and type of blood products transfused in the postoperative period.

Data Analysis

Two outcomes were selected for analysis: (1) severe intraoperative anemia, which was defined as the development of an intraoperative hematocrit level of less than 19%, and (2) excessive postoperative bleeding, which was defined as mediastinal drainage of greater than 1000 mL in the first 12 hours postoperatively. Blood product transfusions and re-exploration have been suggested as surrogates for bleeding,⁹ but there is no consensus regarding the criteria for transfusion² or reoperation.^{19,20} These outcomes were also chosen as potential outcomes that would be important triggers for transfusion that would decrease, although not completely control, the effect of variability in practice.

The postoperative period was defined as the time in the ICU up to a maximum of 3 days for patients who stayed longer in the ICU. The perioperative period was defined as the intraoperative and postoperative periods combined. Patients having their procedure performed off pump were analyzed separately.

Differences between patients who did or did not have the 2 major outcomes were tested for statistical significance by using the Student *t* test for normally distributed data and the Wilcoxon rank test for nonnormal continuous data, whereas χ^2 tests were used for categorical variables. Multivariate logistic regression was performed to obtain adjusted estimates of the odds with 95% confidence intervals of patient, procedure, and provider factors associated with the development of intraoperative anemia and excessive postoperative bleeding. Variables were included in the multivariate models if they were significantly associated or if there was evidence of a substantial effect on univariate analysis, as well as clinical factors associated with transfusions in previous studies. A nested model was used (PROC GENMOD-SAS) in which the surgeons using the same intraoperative initial circuit volume and similar type of antifibrinolytic agent were compared with each other to assess the independent effect of surgeon. Statistical testing was performed with SAS 8.2 (SAS Institute, Cary, NC).

Results

The preoperative variables of the 545 patients undergoing CABG with extracorporeal circulation were similar among the 3 hospitals (Table 1), and data from all 3 hospitals were subsequently combined. The proportion of patients receiving aspirin and heparin preoperatively was significantly different at the 3 sites, with corresponding differences in the preoperative coagulation profile. Intraoperative pump time and the number of grafts were also different. In hospital A, which used larger circuit and HES volumes, significantly more patients had severe intraoperative anemia, but fewer had excessive postoperative bleeding. Hospital C had the lowest re-exploration rate, even though it had the highest proportion of patients with excessive postoperative bleeding.

TABLE 1. Preoperative, intraoperative, and postoperative characteristics and outcomes of all patients in the 3 hospitals

	Hospital A	Hospital B	Hospital C	P value
No. of patients	214	189	142	
Age, y (mean [SD])	66.4 (10.2)	66.3 (10.2)	65.2 (9.6)	NS
Female sex, n (%)	48 (22)	46 (24)	38 (27)	NS
Body surface area (mean [SD])	1.88 (0.22)	1.90 (0.21)	1.88 (0.28)	NS
Parsonnet score (mean [SD])	10.7 (9.5)	10.2 (8.6)	9.5 (6.9)	NS
Patient with score >20, n (%)	30 (14)	30 (16)	11 (8)	.04
Medical history				
Previous cardiac surgery, n (%)	8 (3.8)	5 (2.6)	7 (5)	NS
Preop hematology				
Hemoglobin (mean [SD])	133.5 (15.9)	133.1 (15.6)	134.6 (18.5)	NS
Platelet count (mean [SD])	246 (66)	225 (73)	246 (73)	.003
INR (mean [SD])	1.07 (0.10)	1.14 (0.31)	1.07 (0.16)	<.001
PTT (mean [SD])	45 (27)	54 (39)	41 (29)	.001
Preop medications				
Heparin (full dose), n (%)	49 (23)	109 (58)	68 (48)	.02
Aspirin, n (%)	172 (81)	92 (49)	104 (73)	.001
Intraop variables				
No. of grafts (mean [SD])	3.1 (0.9)	3.6 (1.1)	3.8 (1.1)	.001
Bypass time, min (mean [SD])	77 (27)	87 (32)	90 (35)	.001
Tranexamic acid, n (%)	8 (4)	174 (92)	140 (99)	.001
Aprotinin, n (%)	161 (76)	6 (3)	0	
No antifibrinolytic agent, n (%)	44	9 (5)	2 (1)	
Pump volume added initially				
Total	2000	1400	1400	
Colloid	750	500	500	
Postop variables				
Platelet count (mean [SD])	148 (60)	147 (62)	142 (54)	NS
INR (mean [SD])	1.60 (0.24)	1.36 (0.24)	1.28 (0.28)	<.001
PTT (mean [SD])	45 (13)	40 (23)	56 (41)	<.001
Outcomes				
Intraop HCT				
Lowest (mean [SD])	20.6 (4.4)	22.4 (3.5)	21.4 (4.0)	<.0001
Patients with HCT <19%, n (%)	65 (30)	32 (17)	34 (24)	.006
Postop drainage in the first 12 h				
Mean (SD)	765 (615)	800 (555)	965 (730)	.01
Patients bleeding >1 L, n (%)	42 (20)	47 (25)	50 (35)	.005
Patients transfused, n (%)	110 (51)	89 (46)	83 (51)	NS
Hemoglobin at ICU discharge (mean [SD])	95 (13)	100 (14)	100 (11)	<.001
Length of stay, d				
In ICU (mean [median])	2.2 (1)	3.2 (1)	2.2 (1)	NS
Total in hospital (mean [median])	9.5 (7)	11.7 (7)	10 (7)	NS
Re-exploratory surgery, n (%)	8 (3.7)	14 (7.4)	2 (1.4)	.008
Died, n (%)	4 (1.9)	7 (3.7)	6 (4.2)	NS

SD, Standard deviation; NS, not significant; INR, international normalized ratio; PTT, partial thromboplastin time; HCT, hematocrit; ICU, intensive care unit.

In total, 131 (24%) of the 545 patients whose procedures were performed on pump had severe intraoperative anemia. In univariate analysis this was significantly more likely in older female patients and patients with a lower body surface area and lower preoperative hemoglobin levels. Intraoperative anemia was also associated with higher Parsonnet scores or receipt of larger total volume and larger volumes of colloid in the extracorporeal circuit (Table 2) but not with

use of aprotinin or tranexamic acid. The occurrence of intraoperative anemia by surgeon varied from 18% to 49% (Figure E1). Patients who had intraoperative anemia were more likely to be transfused packed cells (Figure E2), had lower ICU discharge hemoglobin levels, longer hospital and ICU lengths of stay, and higher mortality; however, they did not have an increased frequency of excessive postoperative bleeding.

TABLE 2. Comparison of characteristics and outcomes between patients who did and did not have the lowest intraoperative hematocrit level of less than 19% in patients whose procedures were performed on pump

	Lowest intraop HCT $\geq$ 19%	Lowest intraop HCT <19%	RR (95% CI) or <i>P</i> value
No. of patients	414	131	
Age, y (mean [SD])	65 (10)	69.7 (9.6)	<.001
Female sex, n (%)	61 (15)	71 (31)	3.7 (2.8-4.9)
Body surface area (mean [SD])	1.93 (0.22)	1.75 (0.2)	<.001
Parsonnet score (mean [SD])	9.3 (7.5)	13.2 (10.8)	<.001
Patient with score >20, n (%)	41 (10)	31 (24)	2.0 (1.5-2.8)
Medical history			
Previous cardiac surgery, n (%)	12 (3)	8 (6)	2.1 (0.9-5.0)
LVEF <50%, n (%)	117 (28)	36 (27)	1.0 (0.7-1.3)
Preop hematology			
Hemoglobin (mean [SD])	137.2 (15.4)	122.5 (15.1)	<.001
Platelet count (mean [SD])	235 (73)	250 (62)	.01
INR (mean [SD])	1.1 (0.7)	1.1 (0.4)	NS
PTT (mean [SD])	47 (32)	47 (33)	NS
Preop medications			
Heparin (full dose), n (%)	175 (42)	51 (39)	0.9 (0.7-1.2)
Aspirin, n (%)	275 (66)	93 (71)	1.2 (0.8-1.6)
Intraop variables			
No. of grafts (mean [SD])	3.5 (1.1)	3.4 (1.0)	NS
Bypass time, min (mean [SD])	82 (30)	89 (36)	NS
Tranexamic acid, n (%)	253 (61)	69 (53)	0.8 (0.6-1.0)
Aprotinin, n (%)	123 (30)	44 (33)	1.1 (0.8-1.6)
No antifibrinolytic agent, n (%)	38 (9)	18 (14)	1.4 (0.9-2.1)
Pump volume added initially			
Total (mean [SD])	1614 (288)	1697 (301)	.004
Colloid (mean [SD])	383 (463)	522 (477)	.003
Outcomes			
Intraop transfusions of packed cells			
No. of units transfused (mean [SD])	0.6 (1.4)	2.2 (2.6)	<.001
Patients transfused, n (%)	109 (26)	98 (75)	2.8 (2.1-3.8)
Postop drainage in first 12 h			
Mean [SD]	818 (629)	865 (640)	NS
Patients with >1 L drainage			
Postop transfusions of packed cells, n (%)	99 (24)	41 (31)	1.3 (1.0-1.8)
No. of units transfused (mean [SD])	0.7 (1.8)	1.8 (3.0)	.0001
Patients transfused, n (%)	97 (23)	74 (56)	2.8 (2.1-3.8)
Total intraop and ICU postoperative transfusions			
No. units transfused (mean [SD])	1.4 (2.6)	4.0 (4.3)	<.0001
Patients transfused, n (%)	166 (40)	116 (88)	7.2 (4.3-12)
ICU discharge hemoglobin	99 (13)	93 (13)	<.0001
Length of stay, d			
ICU (mean [median])	2.4 (1)	3.4 (2)	.007
Total in hospital (mean [median])	9.9 (7)	12.1 (8)	.003
Re-exploratory surgery, n (%)	16 (3.9)	8 (6.1)	1.6 (0.7-3.6)
Died, n (%)	9 (2.2)	8 (6.1)	2.8 (1.1-7.1)

HCT, Hematocrit; *RR*, risk ratio; *CI*, confidence interval; *SD*, standard deviation; *LVEF*, left ventricular ejection fraction; *INR*, international normalized ratio; *PTT*, partial thromboplastin time; *ICU*, intensive care unit.

Of the 68 other patients who had their procedures performed off pump and therefore would not have received any priming volumes, only 3 (4%) had intraoperative anemia (data not shown).

Excessive postoperative hemorrhage occurred in 26% of the patients whose procedures were performed on pump. The only preoperative patient characteristic associated with excessive postoperative bleeding in univariate analysis was

TABLE 3. Comparison of characteristics and outcomes between patients who had less than or more than 1 L of mediastinal drainage in the first 12 hours postoperatively in patients whose procedures were performed on pump

	Drainage <1 L	Drainage >1 L	RR (95% CI) or P value
No. of patients	405	140	
Age, y (mean [SD])	66.4 (10)	65.0 (10)	NS
Female sex, n (%)	112 (28)	20 (14)	0.5 (0.3-0.8)
Body surface area (mean [SD])	1.89 (0.22)	1.89 (0.26)	NS
Parsonnet score (mean [SD])	10.4 (8.5)	9.7 (8.8)	NS
Patients with score >20, n (%)	52 (13)	19 (14)	1.1 (0.6-1.7)
Medical history			
Previous cardiac surgery, n (%)	15 (3.7)	5 (3.5)	1.0 (0.4-2.6)
LVEF <50%, n (%)	109 (27)	44 (31)	1.2 (0.9-1.6)
Preop hematology			
Hemoglobin (mean [SD])	132 (16.2)	136 (17)	.05
Platelet count (mean [SD])	236 (68)	245 (77)	NS
INR (mean [SD])	1.1 (0.1)	1.1 (0.4)	NS
PTT (mean [SD])	47 (30)	47 (37)	NS
Preop medications			
Heparin (full dose), n (%)	174 (43)	52 (37)	0.8 (0.6-1.1)
Aspirin, n (%)	272 (67)	96 (68)	1.1 (0.8-1.4)
Intraop variables			
No. of grafts (mean [SD])	3.4 (1.1)	3.7 (1.0)	.007
Bypass time, min (mean [SD])	81 (2.7)	92 (39)	.001
Tranexamic acid, n (%)	229 (56)	92 (66)	1.4 (1.0-1.9)
Aprotinin, n (%)	141 (35)	26 (19)	0.5 (0.4-0.8)
No antifibrinolytic agent, n (%)	35 (9)	22 (15)	1.6 (1.1-2.3)
Lowest intraop HCT (mean [SD])	21.5 (4.0)	21.2 (4.1)	NS
Patients with intraop HCT <19%, n (%)	90 (22)	41 (29)	1.3 (1.0-1.8)
Transfused any packed cells in OR, n (%)	139 (34)	68 (48)	1.5 (1.2-2.0)
Mean no. of units transfused (mean [SD])	0.7 (1.2)	1.7 (2.9)	<.0001
Postop variables			
Platelet count (mean [SD])	147 (58)	144 (63)	NS
INR (mean [SD])	1.1 (0.3)	1.1 (0.1)	NS
PTT (mean [SD])	47 (33)	47 (29)	NS
Outcomes			
Postop transfusions of packed cells			
No. of patients transfused, n (%)	91 (22)	80 (57)	2.9 (2.2-3.9)
No. of units transfused (mean [median])	0.5 (0)	2.5 (1)	<.0001
Total intraop and ICU postop transfusions			
No. of units transfused (mean [SD])	1.2 (1.9)	4.2 (5.1)	<.0001
Patients transfused, n (%)	181 (45)	101 (72)	3.0 (2.1-4.4)
ICU discharge hemoglobin (mean [SD])	99 (13)	93 (12)	<.001
Length of stay, d			
ICU (mean [median])	2.2 (1)	3.7 (2)	<.001
Total in hospital (mean [median])	10.1 (7)	11.1 (7)	NS
Re-exploratory surgery, n (%)	4 (1)	20 (14)	14.5 (5.0-42)
Died, n (%)	6 (1.5)	11 (8)	5.3 (2.0-14.1)

RR, Risk ratio; CI, confidence interval; SD, standard deviation; LVEF, left ventricular ejection fraction; INR, international normalized ratio; PTT, partial thromboplastin time; HCT, hematocrit; OR, operating room; ICU, intensive care unit.

male sex (Table 3). Excessive postoperative bleeding was more likely with longer bypass time, higher number of grafts performed, and certain surgeons (Figure E3) and less likely if aprotinin or tranexamic acid was used. Bleeding was not associated with preoperative aspirin or heparin or with coagula-

tion parameters measured immediately postoperatively. Patients with excessive postoperative bleeding were more likely to be transfused packed cells (Figure E4), had longer ICU lengths of stay, were more likely to undergo re-exploratory surgery, and were more likely to die.

TABLE 4. Multivariate analysis of factors associated with the development of intraoperative anemia and excessive postoperative bleeding in patients whose procedures were performed on pump*

Characteristics	Lowest intraop HCT <19%, adjusted odds ratio (95% CI)	Mediastinal drainage >1 L in the first 12 postop hours, odds ratio (95% CI)
Older age (increase of 5 [eg, 65-70])	1.1 (0.9-1.2)	0.9 (0.8-1.0)
Female sex	3.7 (2.1-6.5)	0.4 (0.2-0.7)
Lower preoperative hemoglobin (decrease of 10)	1.6 (1.4-1.9)	0.9 (0.8-1.05)
Lower body surface area (decrease of 0.1)	1.2 (1.1-1.4)	0.9 (0.8-1.0)
Longer bypass time (increase of 30 min)	1.4 (1.1-1.8)	1.6 (1.3-2.0)
Heparin	0.7 (0.4-1.2)	0.8 (0.5-1.3)
Aspirin	1.3 (0.7-2.3)	1.1 (0.5-1.8)
Aprotinin	0.6 (0.3-1.4)	0.2 (0.1-0.7)
Tranexamic acid	1.9 (0.3-7.9)	0.6 (0.2-1.6)
High pump volumet	15.5 (3.2-73)	0.5 (0.1-2.6)
Surgeons†		
Group 1		
Surgeon 1	1.0 (reference)	1.0 (reference)
Surgeon 2	0.7 (0.2-1.9)	6.9 (1.6-30)
Surgeon 3	0.5 (0.2-1.5)	5.3 (1.3-21)
Surgeon 4	0.5 (0.2-1.4)	8.7 (2.1-36)
Group 2		
Surgeon 5	1.0 (reference)	1.0 (reference)
Surgeon 6	2.0 (0.8-5.4)	3.3 (1.5-7.4)
Surgeon 7	1.4 (0.5-3.7)	4.4 (2.0-9.7)
Surgeon 8	2.2 (0.7-6.4)	2.8 (1.2-6.8)

HCT, Hematocrit; CI, confidence interval. *Bold values indicate significant associations, $P < .05$. †High pump volume: 750 pentastarch of total of 2000 priming volume. ‡Surgeons compared only with other surgeons using similar institutional practices of initial volume of fluid and colloid added to extracorporeal circulation and antifibrinolytic agent: group 1, 750 mL pentastarch of a total of 2000 mL of priming volume; group 2, 500 mL of pentastarch of total of 1400 mL of priming solution.

Eighteen (25%) of 68 patients whose procedures were performed off pump, a similar proportion to the population with operations performed on pump, had excessive postoperative hemorrhage (data not shown).

In multivariate analysis (Table 4) of patients whose procedures were performed on pump, factors associated with intraoperative anemia were those that might reflect greater hemodilution, such as female sex, smaller body surface area, lower preoperative hemoglobin level, and larger initial total and colloid volume in the bypass circuit.

None of these factors were associated with postoperative bleeding. In contrast, excessive postoperative hemorrhage was associated with male sex and was less likely in patients who received aprotinin. After adjusting for these factors, certain surgeons had significantly higher rates of postoperative bleeding. When multivariate linear analyses were performed evaluating blood loss and lowest intraoperative anemia as continuous variables, the same factors were significantly associated as were associated with the excessive postoperative hemorrhage and severe intraoperative anemia as defined dichotomously.

Severe intraoperative anemia was a stronger predictor of packed cell transfusions, whereas excessive postoperative hemorrhage was a stronger predictor of receiving coagula-

tion factors. Of the patients who had severe intraoperative anemia, 88% were transfused packed cells perioperatively compared with 72% who had excessive postoperative hemorrhage, whereas of the patients who met the criteria for excessive postoperative hemorrhage, 50% received fresh frozen plasma and 33% received platelets compared with only 27% receiving fresh frozen plasma and 17% receiving platelets among the patients with intraoperative anemia (Table 5).

Discussion

We have shown that intraoperative anemia and excessive bleeding were associated with different risk factors and appear to be independent phenomena. Both were common and associated with worse outcomes and increased blood product transfusion. Some of the risk factors found are potentially modifiable, which suggests that efforts could be undertaken to decrease the frequency of these 2 entities and thereby possibly improve outcomes in patients undergoing CABG.

One important inference from these results is that perioperative blood product requirements in cardiac surgery might not all be due to excessive bleeding. Patients who had intraoperative anemia had the same mean volume of mediastinal drainage postoperatively as patients who did not

TABLE 5. Comparison of different blood product use in patients undergoing CABG on pump with intraoperative hematocrit levels of less than 19 g/L or mediastinal drainage of greater than 1 L

Periop blood products	Lowest intraop HCT <19%	Mediastinal drainage >1 L	Anemia vs bleeding,
	vs ≥19%, RR (95% CI)	vs <1 L in the first 12 h, RR (95% CI)	RR (95% CI)
No. of patients	131	140	
Packed cells	7.2 (4.3-12)	3.0 (2.1-4.4)	2.8 (1.5-5.3)
Fresh frozen plasma	1.6 (1.2-2.2)	4.4 (3.5-5.7)	0.6 (0.4-0.9)
Platelets	1.4 (0.9-2.0)	3.3 (2.6-4.3)	0.6 (0.4-0.8)

HCT, Hematocrit; RR, risk ratio; CI, confidence interval.

have intraoperative anemia, and less than one third had excessive postoperative bleeding. Many patients who had intraoperative anemia in this study received a transfusion both in the operating room and postoperatively.^{21,22} The differences in the use of coagulation factors associated with mediastinal drainage compared with severe intraoperative anemia also support the hypothesis that clinicians are responding differently to the 2 transfusion triggers.

In this study the strong association of intraoperative anemia with female sex, lower preoperative hemoglobin level, smaller body surface area, and larger total and colloid volume in the initial pump priming solution suggests that hemodilution was an important contributor to this problem. This is also supported by the almost negligible risk (4%) in patients undergoing off-pump procedures. The occurrence of intraoperative anemia has been shown to be an independent predictor of perioperative mortality and morbidity,^{4,6} and strategies to decrease its occurrence might improve outcomes in this population. These strategies would include first decreasing preoperative anemia with practices such as limiting preoperative²³ blood taking, use of more micro-laboratory techniques, and iron supplementation and perhaps erythropoietin in patients awaiting elective operations. Second, because of the strong association with the larger volumes of priming solution with higher volumes of colloid in the extracorporeal circuit, the volume should be adjusted, taking into consideration patient size, sex, and preoperative hemoglobin concentration, rather than using a fixed volume.

This is supported by previous reports^{24,25} of decreases in intraoperative packed cell use with the use of lower prime volume. In a recent study,²⁶ use of hetastarch increased the likelihood of patients undergoing coronary artery surgery receiving 3 or more units of any blood product. The hetastarch might have contributed to greater hemodilution and lower intraoperative hematocrit levels, as well as increased bleeding.²⁶ In our study, higher pump volumes and use of more colloid was strongly associated with intraoperative anemia but not with excessive postoperative bleeding. In the study hospitals, the medium-molecular-weight starches (Pentastan; Bristol Myers Squibb Canada), for which there are less data on increased bleeding risk, are used.²⁷ The doses of

hetastarch used during bypass were fixed and in most patients were less than 15 mL/kg.

Although excessive postoperative hemorrhage has been reported to be one of the most common complications of cardiac surgery,¹² relatively few studies have examined this outcome^{11,28} because most studies examined perioperative transfusions. It has been suggested that outcomes related to excessive drainage should be examined, such as re sternotomy²⁹ and blood product transfusions; our results highlight the limitations of this approach. We noted marked differences in reoperation rates and blood product use in the 3 study sites, which were not related to rates of postoperative bleeding (Table 1) but might reflect practice differences. Therefore, analysis of factors associated with the amount of postoperative bleeding was less likely to be biased than analysis of factors associated with these management decisions. In addition, because postoperative bleeding was associated with longer ICU lengths of stay, transfusions, and a higher mortality, we believe this definition is clinically relevant. In addition, measurement of postoperative mediastinal drainage is objective, routinely performed, and reproducible.

In a prospective study of more than 10,000 patients undergoing cardiac surgery, patient characteristics were not associated with reoperation for postoperative bleeding.³⁰ The authors suggested that reoperation for bleeding might be more related to technical surgical factors rather than patient-related factors. Two other studies have demonstrated that postoperative hemorrhage was associated with surgeon,^{11,13} and meticulous surgical technique is frequently mentioned¹⁶ as an important means to decrease blood product use in cardiac surgery. These findings are consistent with ours, in which male sex was the only patient characteristic and surgeon was strongly associated with this outcome. We speculated that the association with male sex might have occurred because of the assumption that female subjects have higher bleeding risks, which might have resulted in more meticulous surgical practices in female subjects.

We attempted to include in the multivariate analysis the important factors believed to be associated with increased risk of bleeding and transfusion requirements, as well as the factors that differed among the 3 hospitals. There might be

other unmeasured factors that we did not account for that could explain some of the results. Certain variables were also very tightly correlated, such as antifibrinolytic use, volume of prime used in the extracorporeal circuit, and particular surgeon, which limit some of the inferences that can be drawn from the results. In this study neither larger total circuit volumes nor larger HES volumes were associated with excessive mediastinal drainage. Although there have been recommendations that HES not be used in patients undergoing cardiac surgery because of concerns of excess bleeding, we did not find that association in this study, even after adjusting for many clinical variables. The almost exclusive use of aprotinin by the center using the larger volumes of HES might account for our not finding an effect.

There were very few patients who had been exposed to clopidogrel, and no patient had been prescribed low-molecular-weight heparin. We also studied only patients who had bypass procedures alone, without any valvular procedures, and therefore the conclusions might not be applicable to these patient populations. Although repeat surgical interventions were not associated with an increased risk of bleeding in this study, the study might have been underpowered to evaluate this association.

Conclusions

Our results suggest that many factors contribute to triggers to blood product transfusion in cardiac surgery. Reducing these triggers requires different strategies, including methods to decrease hemodilution, especially in small female subjects who might have anemia before surgical intervention. This could include identification and treatment of preoperative anemia and re-evaluation of the design of the bypass circuit. Adjustment of prime volumes with less HES use and use of techniques such as retrograde autologous prime might also be beneficial. On the other hand, postoperative bleeding can be reduced with the use of aprotinin. However, given the association of surgeon with this outcome in this study, meticulous surgical technique appears to be critical to decreasing excessive postoperative bleeding.

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Figure E1. Proportion of patients with intraoperative anemia by hospital and surgeon.

Figure E2. Proportion of patients transfused on the basis of lowest recorded hematocrit level.

Figure E3. Comparison of proportion of patients who had mediastinal drainage of greater than 1 L in the first 12 hours by hospital and surgeon.

Figure E4. Proportion of patients transfused on the basis of volume of mediastinal drainage in the first 12 hours postoperatively.