Coagulation Tests During Cardiopulmonary Bypass Correlate With Blood Loss in Children Undergoing Cardiac Surgery

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Objectives: **To examine whether coagulation tests, sampled before and during cardiopulmonary bypass (CPB), are related to blood loss and blood product transfusion requirements, and to determine what test value(s) provide the best sensitivity and specificity for prediction of excessive hemorrhage.**

Design: **Prospective.**

Setting: **University-affiliated, pediatric medical center.**

Participants: **Four hundred ninety-four children.**

Interventions: **Coagulation tests.**

Measurements and Main Results: **Demographic, coagulation test, blood loss, and transfusion data were noted in consecutive children undergoing cardiac surgery. Laboratory tests included hematocrit (Hct), prothrombin time, partial thromboplastin time (PTT), platelet count, fibrinogen concentration, and thromboelastography. Stepwise linear regression analysis indicated that platelet count during CPB was the variable most significantly associated with intraoperative blood loss (in milliliters per kilogram) and 12-hour chest tube output (in milliliters per kilogram). Other independent variables associated with blood loss were thromboelastography maximum amplitude (MA) during CPB, preoperative PTT, preoperative Hct, and preoperative thromboelastography angle and shear modulus values. Thromboelastography MA during CPB was the only variable associated with total products transfused (in milliliters per kilogram). Of all tests studied, platelet count during CPB (≤108,000/μL) provided the maximum sensitivity (83%) and specificity (58%) for prediction of excessive blood loss (receiver operating characteristic analysis). Blood loss was inversely related to patient age; neonates received the most donor units (median, 8 units; range, 6 to 10 units).**

Conclusions: **During cardiac surgery, coagulation tests (including thromboelastography) drawn pre-CPB and during CPB are useful to identify children at risk for excessive bleeding. Platelet count during CPB was the variable most significantly associated with blood loss.**

KEY WORDS: children, blood coagulation tests, thromboelastography, heart surgery, cardiopulmonary bypass

BLEEDING AFTER cardiopulmonary bypass (CPB) is an important cause of morbidity and mortality for both adult and pediatric patients.[1,2] In children, the hemostatic derangement incurred is complex and influenced by age, surgery, and disease-related factors.[2-4] Published transfusion algorithms for adult[5] and pediatric patients[2] are based on post-CPB coagulation test results. Some children require prompt transfusion therapy after CPB, and this urgency limits the clinical usefulness of coagulation tests obtained after bypass that have a slow turnover time.[6]

The introduction of point-of-care coagulation tests that provide results relatively quickly has reduced the use of allogenic blood products in adults undergoing cardiac surgery.[7] This institution developed a panel of coagulation tests with relatively brief turnover times that could be performed on heparinized blood obtained during CPB. If validated as predictors of hemostatic function and blood loss after bypass, these tests might provide an early indication of blood component requirements and guide post-CPB coagulation management.

Information about hemostasis and coagulation tests during pediatric cardiac surgery is limited and complicated by the heterogenous nature of the patients with regard to age, physiologic states, and pathologic processes.[6,8] Unfortunately, caution must be exercised when extrapolating from adult data because many differences in post-CPB hemostasis exist between adults and children.[2,3] Correlation between blood coagulation test results after CPB and perioperative blood loss in adults has been shown in some studies, but the usefulness of these tests as predictors of blood loss remains controversial.[9-11]

This study of children was designed to examine whether coagulation test results, sampled before and/or during CPB, are related to blood loss and blood product transfusion requirements; and to determine which test value(s) provide the best sensitivity and specificity for prediction of excessive hemorrhage.

METHODS

After institutional review board approval, information pertaining to perioperative hemostasis and its management was obtained prospectively on 494 consecutive children who underwent cardiac surgery at Children's Hospital and Regional Medical Center (Seattle, WA) from January 1996 to December 1997. Demographic data and information about the patient's preoperative clinical status, anesthesia and surgery, and postoperative clinical course were collected. Patients receiving prophylactic antifibrinolytic therapy were excluded from the study.

Anesthetic technique consisted primarily of fentanyl, 25 to 100 μg/kg; midazolam, 0.1 to 0.4 mg/kg; and muscle relaxants (vecuronium, 0.1 mg/kg, and/or pancuronium, 0.1 mg/kg), occasionally supplemented with volatile anesthetic agents. Anticoagulation was established with an initial bolus (infants <1 year, 400 U/kg; children >1 year, 300 U/kg) of porcine heparin (Elkins-Sinn Inc, Cherry Hill, NJ). Additional heparin was administered during CPB to maintain celite activated coagulation time (ACT) at greater than 480 seconds. Anticoagulation was empirically reversed using an initial protamine dose of 3 to 5 mg/kg.

Nonpulsatile CPB was performed with a hollow-fiber membrane oxygenator (Terumo Corporation, Tokyo, Japan). The CPB circuit contained added heparin (3.2 ± 0.9 U/mL, dose depended on prime volume). Prime volumes ranged from 375 to 2,050 mL, depending on patient size. When necessary, blood was added to maintain a hematocrit (Hct) near 20% during CPB. Hypothermia was induced in all patients.

Blood conservation techniques included modified venovenous ultrafiltration (Minntech HPH 400 filter; Minntech Corporation, Minneapolis, MN) for patients aged younger than 1 year and red blood cell salvage (Cell Saver; Haemonetics Corporation, Braintree, MA) for older patients.

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Laboratory tests drawn at the following times included: time point 1 (before surgery), prothrombin time (PT) and international normalized ratio (INR), activated partial thromboplastin time (PTT), platelet count, fibrinogen concentration, and Hct; time point 2 (before CPB), thromboelastography and ACT; time point 3 (15 minutes after initiation of CPB), thromboelastography (with in vitro addition of protamine), platelet count, fibrinogen concentration, Hct, and ACT; and time point 4 (on admission to the intensive care unit [ICU]), PT, INR, PTT, platelet count, fibrinogen concentration, Hct, ACT, thromboelastography, thrombin time, and D-dimers. If products were being transfused at the time of patient admission to the ICU, sampling for time point 4 was delayed until completion of hemostatic therapy.

Blood was aspirated from the patient's indwelling arterial catheter after the withdrawal of five dead-space volumes to prevent contamination by heparin flush. Samples for thromboelastography, PT, PTT, fibrinogen, and D-dimer assays were anticoagulated with sodium citrate; blood samples for platelet count and Hct were anticoagulated with heparin. Laboratory analysis has been described previously.[8]

Thromboelastography analysis was performed using a preheated (37°C) metal cuvette of a Haemoscope Thrombelastograph Coagulation Analyzer (Haemoscope Corp, Skokie, IL). Samples were recalcified by the addition of 250 μL of whole blood to 100 μL of 0.625% calcium chloride. Thromboelastography values measured included reaction time (R), coagulation time (K), angle (α), maximal amplitude (MA), and whole blood clot lysis index at 30 minutes (LY30). The elastic shear modulus (G = [5000]MA/100 − MA) was calculated because it increases exponentially in proportion to the amplitude and may be a sensitive measure of clot strength.[12]

Thromboelastography during CPB, with protamine sulfate added in vitro to neutralize the anticoagulant effects of heparin, has been validated.[13] Protamine (10 μL of 500 μg/mL) was added to 250 μL of whole citrated blood (final protamine concentration, 20 μg/mL of blood) for 1 minute, and the thromboelastography trace was then initiated in the usual manner. An in vitro protamine concentration of 20 μg/mL completely reversed blood containing less than 4 U/mL of heparin[13] and therefore was appropriate for the range of heparin concentrations (2.0 ± 0.6 U/mL) typically achieved during CPB at this institution when using the present study's anticoagulation protocol.[14]

Total blood loss represented the sum of intraoperative and postoperative blood loss. Intraoperative blood loss per kilogram of body weight was calculated as follows:

$$\text{intraoperative blood loss (mL/kg)} = \frac{\left\{\begin{array}{l}\text{swab weight change (g)} \\ \quad + \text{[discard suction volume (mL)} - \text{irrigation volume (mL)]} \\ \quad + \text{chest tube output at end of operation (mL)} \\ \quad + \text{total intraoperative volume of salvaged washed red cells (mL)}\end{array}\right\}}{\text{body weight (kg)}}.$$

Postoperative blood loss per kilogram of body weight was calculated from the sum of chest tube output (mL)/body weight (kg) at 0, 2, 6, 12, and 24 hours after arrival in the ICU.

After consideration of the patient's hemodynamics, Hct, and the rate and volume of blood loss,[15] transfusion therapy was initiated if clinically indicated and was guided by laboratory coagulation test results. Blood components were administered to treat excessive microvascular (coagulopathic) bleeding. When excessive hemorrhage was present during the early post-CPB period, platelet transfusion (1 unit/10 kg) was administered if the platelet count on CPB was less than 100,000/μL, and fresh frozen plasma (1 unit/15 kg) or cryoprecipitate transfusion (1 unit/5 kg) was administered if the fibrinogen concentration on CPB was less than 100 mg/dL. If bleeding continued, further administration of blood products was guided by posttransfusion coagulation test results and followed previously published recommendations.[2] Postoperative minimum acceptable Hct values ranged from 20% to 45%, with the higher values maintained in cyanotic patients. Whole blood (>48 hours old) was used in the early post-CPB period. However, cytomegalovirus-negative (CMV−) products were used for newborns; therefore, many neonates received CMV− packed red blood cells when CMV− whole blood was unavailable. In the late postoperative period, packed red blood cells were transfused to attain the desired Hct if volume overload was a concern. The volume (milliliters per kilogram body weight) of blood products transfused to each patient (intraoperatively and during the first 72 hours after surgery) was prospectively noted.

The authors have previously shown that blood loss correlates inversely with age.[8] Hence, patients were divided into four age groups: group 1, 1 month or younger; group 2, older than 1 to 12 months; group 3, older than 1 to 5 years; and group 4, older than 5 years. Independent continuous data in the multiple age groups were evaluated with a one-way analysis of variance for normally distributed data (expressed as mean ± SD) and Kruskal-Wallis for non–normally distributed data (expressed as median ± 25th to 75th quartiles). The Tukey B test was used to adjust for multiple pairwise comparisons in the analyses of variance. The percentage change from baseline to on-CPB laboratory values was analyzed using Pearson's product moment for possible correlation with degree of hemodilution (prime volume/body weight). Laboratory tests (at sample times 1, 2, and 3) were initially evaluated against blood loss (milliliters per kilogram) and volume transfused (milliliters per kilogram) by Pearson's correlation. Significance was defined as p less than 0.05. Laboratory tests significantly related to blood loss or component transfusions on the univariate analysis were then evaluated by multiple stepwise linear regression. The natural log of patient age in days was used because the range was large and not normally distributed before the log transformation. Criteria for variable inclusion in the stepwise regression analysis were entry for p of 0.05 or less and exclusion for p greater than 0.1. SPSS for Windows (SPSS Inc, Chicago, IL) was used for the calculations.

Excessive blood loss was defined as measured intraoperative loss of 50% or greater of the patient's estimated blood volume (EBV) or postoperative chest tube drainage of 20% or greater of EBV during the initial 2 hours in the ICU (2-hour interval), 20% or greater of EBV from hours 2 to 6 in the ICU (4-hour interval), or 30% or greater during hours 7 to 12 in the ICU (6-hour interval).[15] Using this definition, receiver operating characteristic (ROC) analysis was performed for the variables significantly related to blood loss in the univariate analysis and all laboratory tests sampled during CPB (Med Calc; Med Calc Software, Mariakerke, Belgium). ROC analysis evaluates diagnostic accuracy by changing the laboratory cut point throughout the potential range of the test under study to examine the specificity and sensitivity of the test.[16] Observed values greater than the laboratory cut point are considered positive for the disease (excess bleeding), and values less than the outpoint are considered negative for the disease. The test result in which both sensitivity and specificity together are at a maximum is the value frequently chosen to differentiate normal from the disease state.

RESULTS

Twenty-four patients underwent reexploration of the chest for bleeding. In 12 patients, the cause was large-vessel (surgical) hemorrhage, and these patients were excluded from all data analysis. In the other 12 patients, microvascular (coagulopathic) hemorrhage was considered contributory by the surgeon, and these children were included in data analysis. Selected demographic and intraoperative data of these 482 patients are listed in Table 1.

Laboratory test values at various time points are compared among age groups in Tables 2 and 3. All preoperative values were within laboratory limits of normal, apart from a slightly

Table 1. Patient Demographics and Details of Surgery

	Age Group 1 (≤1 mon)	Age Group 2 (>1-12 mon)	Age Group 3 (>1-5 y)	Age Group 4 (>5 y)	Difference* Among Groups
No. of patients	74	118	161	129	
Sex (men/women)	43/31	67/51	79/82	71/58	
Age (mon)	0.31 ± 0.26	5.5 ± 3.0	32.2 ± 13.5	127.0 ± 54.7	
Weight (kg)	3.4 ± 0.6	5.7 ± 1.7	12.6 ± 3.4	35.8 ± 19.3	
Height (cm)	51 ± 6	62 ± 7	87 ± 14	135 ± 23	
Resternotomy	1 (1)	19 (16)	32 (20)	39(30)	4,3 > 2 > 1
Total heparin (U/kg)	401 ± 101	405 ± 103	367 ± 113	330 ± 75	1,2 > 3 > 4
Total protamine (mg/kg)	5.8 ± 3.1	4.8 ± 2.0	4.1 ± 1.1	3.5 ± 1.9	1 > 2 > 3 > 4
Crystalloid prime	0 (0)	4 (3)	91 (57)	122 (95)	4 > 3 > 2,1
Whole blood prime	36 (49)	94 (80)	57 (35)	6 (5)	2 > 1,3 > 4
Packed red blood cell prime	38 (51)	20 (17)	13 (8)	1 (0)	1 > 2,3 > 4
Prime volume/body wt (mL/kg)	202.8 ± 44.2	131.5 ± 38.7	65.5 ± 18.3	40.5 ± 12.6	1 > 2 > 3 > 4
Ultrafiltration	51 (69)	58 (49)	4 (2)	0 (0)	As per protocol
Cell separation	8 (11)	39 (33)	142 (88)	124 (96)	As per protocol
CPB (min)	140 ± 48	97 ± 53	69 ± 43	81 ± 53	1 > 2 > 3,4
Aortic clamping (min)	57 ± 25	34 ± 27	30 ± 33	40 ± 46	1 > 2,3,4
DHCA (min)	30 ± 30	5 ± 17	0 ± 2	0 ± 6	1 > 2 > 3,4

NOTE. Values expressed as mean ± SD or number (percent).

Abbreviations: CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest.

*Significance set at $p < 0.05$.

prolonged PTT (51 ± 28 seconds) for group 1 patients (normal, 24 to 50 seconds). Some preoperative test values varied with age. Compared with the other groups, group 1 patients were more hypocoagulable (with significantly longer PT, INR, PTT, and thromboelastography K values), and group 2 patients were more hypercoagulable (with significantly shorter PT, INR, and PTT and greater platelet count and thromboelastography MA and G values).

These preoperative age-associated variations in laboratory values were substantially altered by CPB (Table 2). Platelet count, fibrinogen concentration, and thromboelastography α, MA, LY30, and G values all became abnormal during CPB; in

Table 2. Changes in Laboratory Tests (mean values) With Onset of Cardiopulmonary Bypass

Laboratory Tests	Sample Period	Age Group 1 (≤1 mon)	Age Group 2 (>1-12 mon)	Age Group 3 (>1-5 y)	Age Group 4 (>5 y)	ANOVA	Difference* Among Groups
Hematocrit (%)	Pre-CPB	42	40	41	40	NS	
Hematocrit (%)	On CPB	24†	22†	20†	23†	0.0001	3 < 2,4 < 1
Platelet count (K/μL)	Pre-CPB	274	377	302	260	0.0001	4 < 1 < 3 < 2
Platelet count (K/μL)	On CPB	49†	89†	124†	151†	0.0001	1 < 2 < 3 < 4
Fibrinogen (mg/dL)	Pre-CPB	217	208	223	230	NS	
Fibrinogen (mg/dL)	On CPB	85†	89†	86†	114†	0.0001	1,2,3 < 4
Thromboelastography							
R (mm)	Pre-CPB	23	19	19	19	NS	
R (mm)	On CPB	17†	17	19	18	NS	
α (°)	Pre-CPB	46	51	49	51	NS	
α (°)	On CPB	33†	41†	44†	50	0.0001	1 < 2,3 < 4
MA (mm)	Pre-CPB	46	51	46	48	0.0001	1,3 < 4 < 2
MA (mm)	On CPB	24†	32†	34†	41†	0.0001	1 < 2 < 3 < 4
LY30 (%)	Pre-CPB	5.9	4.7	5.9	6.8	0.04	2 < 1,3 < 4
LY30 (%)	On CPB	29.3†	16.8†	9.5†	5.1†	0.0001	1,2 < 3 < 4
G (dynes/cm²)	Pre-CPB	4,546	5,560	4,460	4,761	0.0001	1,3,4 < 2
G (dynes/cm²)	On CPB	1,700†	2,406†	2,672†	3,552†	0.0001	1 < 2,3 < 4
ACT (s)	Pre-CPB	137	128	133	138	0.001	2 < 3,1,4
ACT (s)	On CPB	931†	894†	777†	612†	0.0001	4 < 3 < 2,1
PT‡ (s)	Pre-CPB	15.9	13.4	13.5	14.3	0.0001	2,3 < 4 < 1
INR‡	Pre-CPB	1.4	1.1	1.1	1.2	0.0001	2,3,4 < 1
PTT‡ (s)	Pre-CPB	51	38	38	39	0.0001	2,3,4 < 1
TEG k‡ (mm)	Pre-CPB	12	8	9	8	0.006	2,3,4 < 1

Abbreviations: ACT, activated coagulation time; G, shear modulus; INR, international normalized ratio; LY30, whole-blood clot lysis index at 30 minutes after MA; MA, maximum amplitude; NS, not statistically significant; PT, prothrombin time; PTT, activated partial thromboplastin test; ANOVA, analysis of variance; CPB, cardiopulmonary bypass.

*Significance set at $p < 0.05$.

†Significantly different from pre-CPB values (Student's independent *t*-test, $p < 0.05$).

‡Tests not performed during CPB.

Table 3. Laboratory Tests (mean values) Sampled After Arrival in Intensive Care Unit

Laboratory Tests	Sample Period	Age Group 1 (≤1 mon)	Age Group 2 (>1-12 mon)	Age Group 3 (>1-5 y)	Age Group 4 (>5 y)	ANOVA	Difference* Among Groups
Hematocrit (%)	ICU	43	39	36	33	0.0001	4 < 3 < 2 < 1
PT (s)	ICU	19.6	18.4	18.7	18.9	NS	
INR	ICU	1.9	1.8	1.8	1.8	NS	
PTT (s)	ICU	55	50	45	43	0.001	4,3,2 < 1
Platelet (K/μL)	ICU	219	199	183	186	0.001	3,4,2 < 1
Fibrinogen (mg/dL)	ICU	200	226	181	167	0.001	4,3 < 1 < 2
Thromboelastography							
R (mm)	ICU	14	14	16	15	NS	
K (mm)	ICU	7	11	10	8	NS	
α (°)	ICU	54	51	50	46	NS	
MA (mm)	ICU	51	49	46	44	NS	
LY30 (%)	ICU	1.5	4.2	4.2	3.8	0.02	1 < 2,3,4
G (dynes/cm²)	ICU	5,470	4,547	4,289	3,887	NS	
ACT (s)	Post protamine	146	127	128	125	0.02	2,3,4 < 1

NOTE. Many patients had received blood product transfusions.

Abbreviations: ACT, activated clotting time; G, shear modulus; ICU, intensive care unit; INR, international normalized ratio; LY30, whole blood clot lysis index at 30 minutes after MA; MA, maximum amplitude; NS, not statistically significant; PT, prothrombin time; PTT, activated partial thromboplastin test; ANOVA, analysis of variance.

*Significance set at $p < 0.05$.

contrast, thromboelastography R did not worsen. Correlation between MA and platelet count was $r = 0.68$ and between MA and fibrinogen concentration was $r = 0.47$ (Pearson's product-moment). During CPB, group 1 patients had more prolonged ACTs and more abnormal values for platelet count, fibrinogen concentration, and thromboelastography measurements (α, MA, LY30, and G) than the other age groups. Of the tests performed during CPB, a decrease in platelet count correlated best with hemodilution (Pearson's product-moment, $r = 0.70$). In 105 patients who had a CPB duration longer than 1 hour, a second platelet count during CPB was measured on initiation of rewarming, and this value was 15% less than the first platelet count during CPB ($p < 0.0001$, paired Student's t-test).

Laboratory values after CPB were influenced by blood product transfusions. All group 1 patients received transfusions in the post-CPB period. After arrival in the ICU, these patients had a greater Hct and platelet count, less fibrinolysis (LY30), and a more prolonged PTT than other age groups (Table 3).

Group 1 patients incurred greater measured intraoperative blood loss than other age groups. Postoperative 12-hour chest tube output (milliliters per kilogram) differed significantly with age (group $1 > 2 > 3 > 4$), and the total blood products transfused (milliliters per kilogram) were greater in children aged older than 1 to 12 months than in other age groups (Table 4). Median total units transfused were inversely related to age.

Results of stepwise linear regression analysis of these laboratory test values and (1) intraoperative blood loss, (2) postoperative 12-hour chest tube output, and (3) total products transfused are listed below, with adjusted coefficient of determination (R^2) and correlation indicated as positive [+] or negative [−].

Analysis indicated platelet count during CPB was the variable most significantly associated with intraoperative blood loss ([−], $R^2 = 0.07$). Preoperative PTT [+] was also independently related to intraoperative blood loss. Cumulative adjusted $R^2 = 0.11$.

When tested in the model, patient age ([−], $R^2 = 0.09$) replaced platelet count as the most important variable, whereas preoperative PTT remained an independently related variable. Addition of weight to this second model showed weight was not independently associated with bleeding. Cumulative adjusted $R^2 = 0.12$.

The most important independent variable for 12-hour chest tube output was platelet count during CPB ([−], $R^2 = 0.18$). Other tests independently related to postoperative blood loss included preoperative PTT [+], preoperative G [−], preoperative α [−], MA during CPB [−], and preoperative Hct [+]. Cumulative adjusted $R^2 = 0.29$.

When age was tested in the model, age became the variable most significantly associated with blood loss ([−], $R^2 = 0.28$).

Table 4. Comparison of Intraoperative Blood Loss, Postoperative Chest Tube Output, and Blood Products Transfused (mL/kg and units/patient) for Different Patient Age Groups

	Age Group 1 (≤1 mon)	Age Group 2 (>1-12 mon)	Age Group 3 (>1-5 y)	Age Group 4 (>5 y)	p*
Intraoperative blood loss (mL/kg)	26.0 (12.0-65.6)	20.8 (11.1-37.3)	21.0 (13.9-28.2)	16.9 (11.2-23.4)	0.0001
12-hour chest tube output (mL/kg)	46.3 (25.8-70.0)	31.2 (20.9-47.2)	20.1 (13.3-30.2)	10.8 (6.9-15.6)	0.0001
Total transfused (mL/kg)	48.2 (4.4-48.2)	87.9 (5.1-205.1)	56.2 (0-141.3)	32.3 (0-116.3)	0.04
Total transfused (units)†	8 (6-10)	5 (3-7)	1 (0-4)	0 (0-2)	<0.0001

NOTE. Values expressed as median (25^{th} to 75^{th} quartiles).

*Kruskal-Wallis test.

†All donor units, including whole blood, packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate (both topical and intravenous).

Table 5. Receiver Operating Characteristic Analysis of Laboratory Tests

Laboratory Test	No.	Value	Sensitivity (%)	Specificity (%)	Area ± SE
Thromboelastography LY30, Pre-CPB (%)	339	≤4.4	68	65	0.711 ± 0.037
INR, pre-CPB	468	>1.2	44	79	0.622 ± 0.037
PT, pre-CPB (s)	449	>14	54	70	0.603 ± 0.035
Thromboelastography α, pre-CPB (°)	348	≤33	27	92	0.589 ± 0.039
PTT, pre-CPB (s)	458	>48	27	90	0.573 ± 0.038
Thromboelastography R, pre-CPB (mm)	348	>14	86	30	0.569 ± 0.042
Hematocrit, pre-CPB (%)	454	>44	36	79	0.553 ± 0.035
Platelet, pre-CPB (K/μL)	480	≤190	24	90	0.544 ± 0.034
Thromboelastography G, pre-CPB (dynes/cm²)	345	≤2,937	19	93	0.521 ± 0.041
Platelet, on CPB (K/μL)	474	≤108	83	58	0.727 ± 0.028
Hematocrit, on CPB (%)	477	>23	57	72	0.671 ± 0.037
Thromboelastography G, on CPB (dynes/cm²)	347	≤1,944	46	80	0.668 ± 0.036
Thromboelastography MA, on CPB (mm)	347	≤28	46	80	0.667 ± 0.036
Thromboelastography α, on CPB (°)	350	≤40	53	68	0.625 ± 0.038
Fibrinogen, on CPB (mg/dL)	480	≤85	40	80	0.606 ± 0.033
Thromboelastography LY30, on CPB (%)	322	>11.1	39	80	0.555 ± 0.045
Thromboelastography r, on CPB (mm)	352	>16	68	43	0.550 ± 0.042

Abbreviations: area ± SE, area ± standard error under the ROC curve; G, shear modulus; INR, international normalized ratio; LY30, whole blood clot lysis index at 30 minutes after MA; MA, maximum amplitude; No., number of patients; PT, prothrombin time; PTT, activated partial thromboplastin test; ROC, receiver operating characteristic.

Preoperative G, α, and Hct remained significant, and preoperative platelet count [−] became a significant independent variable. Platelet count and MA during CPB were replaced by α during CPB [−]. Again, weight was not independently associated with chest tube output. Cumulative adjusted $R^2 = 0.39$.

Thromboelastography MA was the only laboratory test significantly associated with total products transfused ([−], $R^2 = 0.02$). Age or weight was not significantly associated with total transfusions.

Study patients were retrospectively grouped into bleeders or nonbleeders for ROC analysis (Table 5). Platelet count on CPB yielded the greatest area under the ROC curve and thus was the best laboratory test for distinguishing patients who were bleeders from nonbleeders. At a value of 108,000/μL or less, platelet count on CPB provided a sensitivity of 83% and specificity of 58%.

DISCUSSION

This study of children undergoing cardiac surgery found that platelet count during CPB correlated inversely with the magnitude of hemodilution and was the test most significantly associated with blood loss. Age was independently associated with blood loss and was a useful surrogate indicator of defective hemostasis. Perturbation of laboratory coagulation tests by CPB was most profound in children aged younger than 1 year. These infants had the greatest perioperative blood loss (milliliters per kilogram) and received the largest volume (milliliters per kilogram) and number of units (median) of allogenic blood products.

Age-associated variations in pre-CPB coagulation tests were similar to those reported previously.[8] The observation that group 1 patients were more likely to have abnormal preoperative laboratory coagulation test results is also consistent with a previous report.[17]

The deleterious effects of CPB on the coagulation system were evident from the markedly abnormal laboratory values during CPB. Hemodilution was clearly important because test values were most deranged in neonates, the group subjected to the greatest hemodilution. It is not surprising that platelet count during CPB correlated best with degree of hemodilution because the whole blood in the CPB prime was greater than 48 hours old and platelet depleted. The platelet count for group 1 (49 ± 32 K/μL) was less than that reported (64 ± 24 K/μL) for 30 neonates who received fresh (<48 hour old) blood in the CPB prime.[17] Over time during CPB, platelet count diminished further and minimum platelet count was less than that predicted by hemodilution. This implies CPB-induced consumption and/or sequestration of platelets, but these effects on platelet count were minor compared with that of hemodilution. Thromboelastography α, MA, and G values are influenced by platelet function and number,[18] and these tests and also platelet count reflected the influence of hemodilution.

The impact of hemodilution on other test values was apparently modified by the use of blood in the CBP prime. Thus, fibrinogen decreased from baseline but did not differ among groups 1, 2, and 3 and was similar to values reported for neonates[17] and older children.[3] Thromboelastography R values did not deteriorate, perhaps indicating soluble coagulation factor activity was collectively sufficient for generation of clot. During CPB, coagulation factors in neonates reportedly decreased by 50% from baseline, with activities ranging from 24% to 31%,[17] and by 56% from baseline in children (median age, 3 years) with some factors (V and VII) less than the generally accepted minimal hemostatic levels.[3]

Clot lysis during CPB was more pronounced in groups 1 and 2. CPB-induced activation of fibrinolysis has been documented in children,[3] and the investigators reported that young children (mean age, 12 months) were more likely to become hyperfibrinolytic during CPB than older children.[19]

Similar to a study of adults,[13] the authors found protamine-reversed thromboelastography values during CPB in children accurately reflected post-CPB thromboelastography values. The

postoperative prolongation of PT and INR observed in all groups has likewise been noted in adults after cardiac surgery data.[20]

The hazards of multiple and massive transfusions with allogenic blood products are well recognized and warrant a critical approach to perioperative management of hemostasis.[9,11] The usefulness of laboratory coagulation test results in predicting blood loss has often been examined by either comparative statistical analysis after assigning patients into groups based on excessive blood loss criteria or linear regression analysis of blood loss and laboratory tests. The authors used both methods.

Platelet count during CPB was the variable most significantly associated with intraoperative blood loss and 12-hour chest tube output. Investigators have cited acquired platelet function abnormalities as the major etiologic factor of bleeding in adults,[21,22] but quantity of platelets may be important in children.[3] Postprotamine platelet count correlated with blood loss in one pediatric study.[6] The authors showed platelet count during CPB correlated with hemodilution. Hemodilution exerts a major influence on the coagulation system in both neonates[18] and older children.[3] The present results suggest reduction in platelet number is perhaps the most important hemostatic defect in children. With regard to patient management, it seems advisable to limit CPB circuit priming volume as much as possible and to restore platelet count toward normality during transfusion therapy.

During CPB, thromboelastography MA correlated better with platelet number than fibrinogen concentration and was independently associated with 12-hour chest tube output and total products transfused. Thromboelastography after CPB is reported useful for predicting excessive postoperative bleeding in adults[23-25] and children[6,26] undergoing cardiac surgery.

Baseline coagulation tests (PTT and thromboelastography) were independently associated with blood loss and therefore are clinically indicated. Cyanotic cardiac disease probably accounted for the positive correlation between Hct and hemorrhage. In contrast to the authors' findings, preoperative laboratory values have not been associated with blood loss after cardiac surgery in adults.[5,24] Hypoxia, liver congestion, and immaturity are relatively common in pediatric patients with congenital cardiac disease and may affect hemostasis.[27] A previous report evaluated coagulation changes after CPB in 75 children and found baseline coagulation test results did not correlate with postoperative chest tube drainage.[6] The greater number of patients in this study (n = 482) may explain this difference.

Early post-CPB transfusion may modify both intraoperative blood loss and postoperative chest tube drainage; hence, total blood products transfused was included as an outcome measure. Results of blood product analysis were similar to those of blood loss analysis, but products transfused did not correlate with any baseline coagulation tests. The possibility that volume transfused exceeded that required for hemostasis cannot be excluded and weakens the usefulness of this outcome measure.

The subdivision of patients into those with and without excessive bleeding was based on frequently recommended chest tube output criteria for considering reexploration of the chest.[16,28] ROC analysis also identified platelet count during CPB as the test most strongly associated with blood loss. The sensitivity (83%) and specificity (58%) of platelet count during CPB ($\leq$108,000/μL) were within the accepted useful range[20] and similar to values recently reported for adults undergoing cardiac surgery (post-CPB platelet count, 102,000/μL; sensitivity, 67%; specificity, 75%).[5] After consideration of Table 5 data and linear regression analyses, the authors propose the following preoperative test values may help identify children at increased risk for bleeding: PTT of 49 seconds or longer, thromboelastography α less than 34°, platelet count less than 190,000/μL, or Hct of 45% or greater.

Cumulative adjusted coefficient of determination for coagulation tests and postoperative blood loss ($R^2 = 0.29$) was at least double that reported for adults undergoing cardiac surgery,[5,9,10] suggesting the more extreme hemostatic derangement encountered in children enhances the utility of coagulation tests. However, the relatively small R^2 underscores the inadequacies of current hemostasis monitoring during cardiac surgery. By comparison, when patient age (as natural log) was added to the model (12-hour chest tube output), age alone accounted for 28% of the variability. This knowledge can be used to good advantage. Age identifies patient groups likely to become coagulopathic and quantifies their blood transfusion requirements. This facilitates hemostatic management strategies. Coagulation tests identify individuals at risk for increased bleeding and guide transfusion therapy. Adjusted cumulative R^2 for 12-hour chest tube output with age and coagulation tests included in the model was 0.39.

The introduction of point-of-care coagulation tests to guide transfusion therapy in the surgical arena has reduced the use of allogenic blood products in adults undergoing cardiac surgery procedures.[29] The benefits of a transfusion algorithm have been shown in adults,[30,31] but it remains controversial as to which tests should be included.[11] The present study indicated patient age and platelet count during CPB are important factors for inclusion in a pediatric cardiac surgery transfusion algorithm.

In conclusion, this prospective study of 482 children showed that laboratory coagulation tests performed before and during CPB were independently associated with perioperative blood loss and volume of blood products transfused. Platelet count during CPB was the variable most significantly associated with blood loss, both by stepwise multiple regression and ROC analysis, with a value of 108,000/μL or less providing the maximum sensitivity and specificity for prediction of excessive hemorrhage. Other independent variables included thromboelastography MA during CPB and several pre-CPB measures (thromboelastography α and G, PTT, Hct). Results of these tests can be made available before termination of CPB, an important advantage during pediatric cardiac surgery because values can guide post-CPB hemostasis management and timely ordering of blood components. Patient age usefully identified pediatric subgroups at increased risk for excessive blood loss and can be used along with laboratory coagulation test results in transfusion algorithms for pediatric cardiac surgery.

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