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Coagulation Changes during Packed Red Cell Replacement of Major Blood Loss

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A greater proportion of blood replacement needs are being met by packed red cell concentrates rather than whole blood in situations of major blood loss. Twelve patients, who required major blood replacement during elective surgery, were studied to determine the changes in coagulation when packed red cells were used to replace major blood loss. In addition, the coagulation abnormalities present at the time an observer noted excessive bleeding were determined. Prior to blood product replacement and after the estimated loss of each 0.3 blood volume, coagulation tests were obtained including prothrombin time (PT), partial thromboplastin time (aPTT), platelet count, thrombin time (TT), fibrinogen levels, and assays of coagulation Factors V, VIII, and IX. Coagulation tests were repeated when clinical hemostasis was judged inadequate by the anesthesiologist and attending surgeon. Significant decreases in platelet count, fibrinogen levels, and Factor V, VIII, and IX levels occurred as increasing blood volumes were replaced. Increases in PT and aPTT above control occurred in nine of the 12 patients prior to replacement of 1 blood volume; none of the nine patients had increased clinical bleeding. In four of seven patients who had blood replacement of greater than 1 blood volume, increased clinical bleeding was noted by the observer. Platelet counts were less than 100,000/mm^3 in each of these four patients, and a platelet concentrate obtained by pheresis of a single donor was administered. In two of the four patients platelet counts increased, but clinical bleeding did not resolve. Fresh-frozen plasma (FFP) in addition to the platelet concentrate was used in these two patients. In both patients fibrinogen levels were less than 75 mg/dl, and the PT and aPTT were 1.5 times control values prior to FFP. If prolongation of PT and PTT had been used as the indication for administration of FFP, nine of the 12 patients would have unnecessarily received FFP prior to the loss of 1 blood volume. In situations when packed red cells are used for major blood replacement, clotting factors in the form of FFP may not be necessary to maintain the PT or PTT at accepted normal levels. (Key words: Blood, coagulation: packed red blood cells. Transfusion, packed red blood cells: coagulation factors.)

IN RESPONSE to a documented increase in the use of fresh-frozen plasma (FFP) and clear evidence of potential risks of disease transmission associated with FFP,[1,2] an NIH consensus panel met in 1984 to determine the current indications for the use of FFP.[3] In situations of massive transfusion, the panel noted that platelets were the most frequently required component when increased bleeding occurred and that the empiric or prophylactic use of FFP did not decrease transfusion requirements. The NIH consensus panel recommended FFP during massive transfusion only when clotting factor deficiency is believed to be the sole or principal hemostatic derangement. The panel also cited a need for more information about the requirements for FFP in situations of massive transfusion.

While the NIH consensus panel recommended whole blood transfusion in situations of major blood loss, many centers use crystalloid solutions and packed red cell concentrates in place of whole blood transfusion to meet volume and red cell requirements in the resuscitation of bleeding patients.[4,5] With new blood preservatives that extend the storage period and viability of packed red cell concentrates, an even greater proportion of erythrocyte replacement needs are currently being met by packed red cell concentrates in acute blood loss situations.[5]

The purpose of this study was to identify coagulation changes that occur during elective surgery when crystalloid solutions and packed red cells stored in Adsol® (Fenwal Laboratories) preservative (adenine, saline, glucose, and mannitol)[6] are used to replace major blood loss. In addition, to determine the minimum coagulation factor levels required for effective surgical hemostasis, coagulation tests were repeated when increased clinical bleeding occurred.

Materials and Methods

After obtaining consent for the protocol from the institution's committee for human studies, ASA physical status II or III patients who required major elective surgery were studied. Informed written consent was not required. Patients were excluded if they had a recent history of trauma or burns, and none of the patients had a history or a physical examination suggestive of a bleeding disorder. A preoperative platelet count, prothrombin time (PT) (normal range, 10–13 s), and activated partial thromboplastin time (aPTT) (normal range, 22–33 s) were performed. Monitoring for the operations included direct arterial pressure measurement, heart rate by ECG, urine

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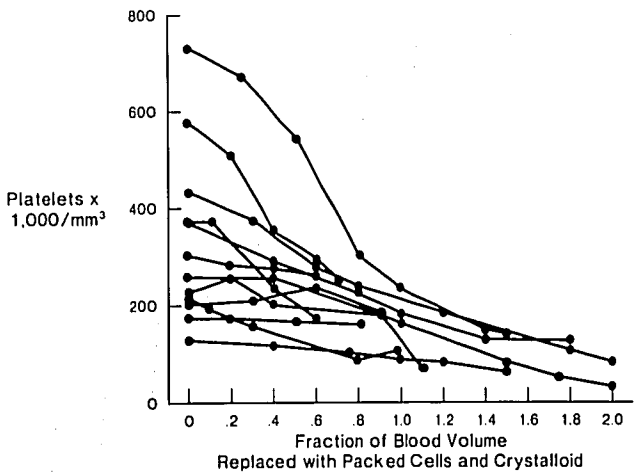

FIG. 1. Decreases in platelet count as increasing blood volumes are replaced with Adsol packed cells and crystalloid solutions. Each patient is represented by a solid continuous line.

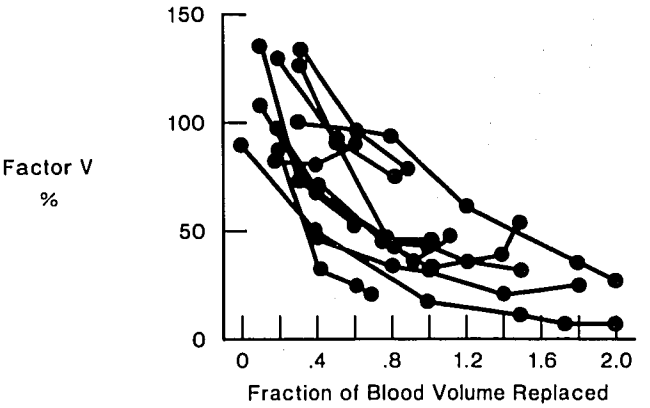

FIG. 3. Decreases in Factor V level as blood volume is replaced with Adsol packed cells and crystalloid solutions. Each patient is represented by a solid line.

output, and central venous and/or pulmonary artery occlusion pressure measurements. All patients received general anesthesia, which included thiopental, fentanyl, isoflurane, and nondepolarizing muscle relaxants.

Following the start of surgery, but prior to any blood product transfusion, coagulation tests were obtained that included platelet count, PT and aPTT, fibrinogen degradation products (FDP), fibrinogen level, and thrombin time (TT) as well as an additional blood sample for later assays of coagulation Factors V, VIII, and IX levels. Coagulation tests were repeated after every one-third blood volume was replaced. Coagulation factor assays were measured later in the 12 patients who required replacement of more than 70% of their estimated blood volume.

Crystalloid solutions were administered to replace estimated fluid losses as judged by central filling pressures, arterial blood pressure, and urine output.[7-9] Additional crystalloid and packed red cells reconstituted with normal saline prior to transfusion were administered to replace observed blood losses with the goal of therapy to maintain a hematocrit of 30.[10] Serial hematocrit determinations and the number of units of packed red cells administered (assuming each unit of packed cells would replace 500 ml of blood loss) were used to confirm the estimates of blood loss.[8,10] Blood samples for analysis were obtained by withdrawing at least five times the tubing volume (5 × 1.2 ml) from a 20-G radial arterial catheter prior to obtaining coagulation studies.[11] Platelet count determinations were available within 40 min of collection. Fibrinogen levels, PT, and aPTT were analyzed and the results made available to the anesthesiologist no more than two hours following collection. Specimens obtained for Factors V, VIII, and IX levels were flash-frozen within 30 min of collection and stored at −80° C for assay at a later date.

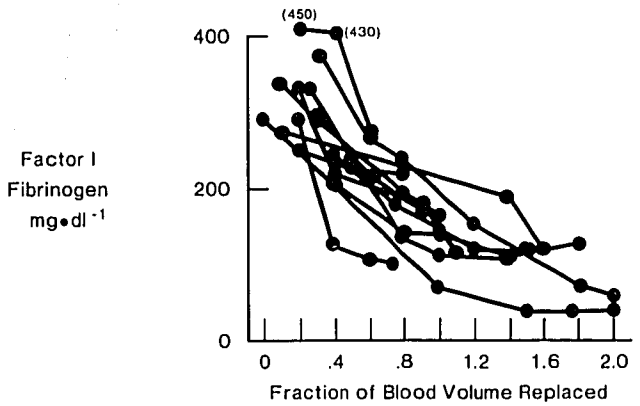

FIG. 2. Decreases in fibrinogen level as blood volume is replaced with Adsol packed cells and crystalloid solutions. Each patient is represented by a solid line.

Coagulation testing included the following: platelet count (Technicon Corp. Model H6000); PT (Thromboscreen, Pacific Hemostasis, Coagulyser, Lancer); aPTT (Automated aPTT, General Diagnostic Corp., Coagulyser, Lancer); thrombin clotting time (TT) (Dade-Fi-American Dade); fibrinogen assay (Dade-Fi, American Dade, Fibrometer, Becton Dickinson); and FDP (Data-Fi, American Dade). Coagulation factor assay for Factors VIII and IX were performed by the one stage assay using the same reagents used for the aPTT. The Factor V assay was performed by the one stage technique using the same reagents used for the PT. Factor assays were performed on the Coagamate Model 2001 (General Diagnostics Corp.).

The quality of hemostasis present at the operative site was observed by the same anesthesiologist (D.J.M.) and the attending surgeon in all patients. If bleeding from wound edges recurred after hemostasis had initially been achieved or if the surgical field was judged to be bleeding

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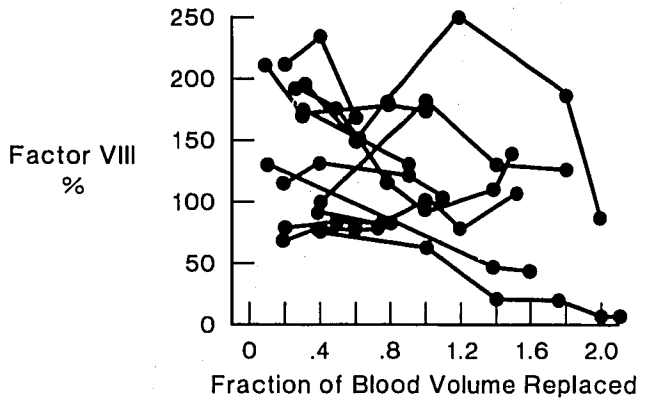

FIG. 4. Changes in Factor VIII level with surgery and increasing blood volume replacement with Adsol packed cells and crystalloid. Each patient is represented by a solid line.

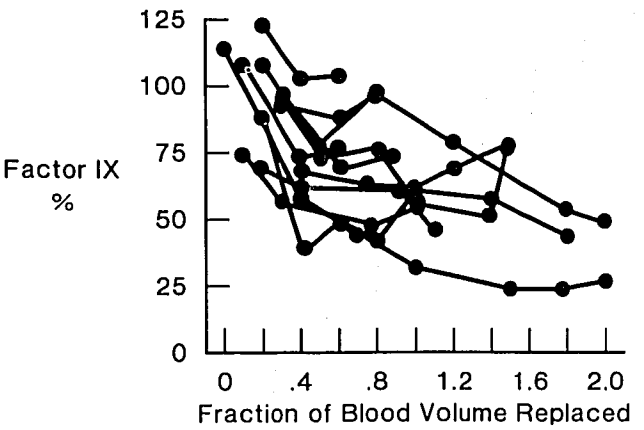

FIG. 5. Changes in Factor IX level with surgery and increasing blood replacement with Adsol packed cells and crystalloid. Each patient is represented by a solid line.

out of proportion to the degree of dissection that had occurred, a repeat set of coagulation measurements was obtained. Component therapy (either platelets or FFP) was withheld until the results of the platelet count were available. In all situations of excessive bleeding the decision to use either platelets or FFP during the study period was based on the platelet count. If platelet counts were less than 100,000/mm^3, a platelet concentrate was administered, and repeat coagulation tests were obtained 20 min later. If following the platelet concentrate additional component therapy was judged necessary on the basis of the quality of hemostasis, FFP was administered to replace approximately 20% of the plasma volume.

Regression analysis was performed to estimate proportional decreases in platelet count and coagulation factor levels in relation to blood volume replaced.[12] The regression analysis was used to create a linear slope between the blood volume replaced and the coagulation factor levels. An estimate of the slope and 95% confidence limits were determined for each of the coagulation levels measured (platelet counts, Factor V, Factor VIII, Factor IX, and fibrinogen), and using the slope from the regression analysis a t test of association between blood volume replaced and the coagulation factor level was used to determine significance ($P < 0.05$).

Results

As greater fractions of blood volume were replaced with packed red cell concentrates and crystalloid solutions, significant decreases in platelet count (fig. 1), fibrinogen (fig. 2), Factor V (fig. 3), VIII (fig. 4), and IX (fig. 5) levels occurred. From the regression analysis an estimate of the expected decrease in clotting factor levels following 1 blood volume replacement was made (table 1). The 95% confidence intervals for each clotting factor and the correlation coefficient (r^2) for each coagulation factor was also obtained from the regression analysis (table 1).

The PT and aPTT increased above control levels prior to replacement of 1 blood volume in nine of the 12 patients. None of the 12 patients manifested any observable bleeding tendency with blood replacement up to and including 1 blood volume. In eight of 12 patients who had no clinical bleeding problems during the operation, the results of the final coagulation tests and blood volume replaced during the operation are presented in table 2. No coagulation components (platelet concentrates or FFP) were considered necessary during the study period in these eight patients.

In four of the seven patients who required greater than 1 blood volume replacement, based on the criteria described to assess clinical hemostasis, excessive bleeding was judged to be present (table 3). In these four patients platelet counts were less than 100,000/mm^3 and the PT and aPTT levels were elevated (table 3). Platelets corrected the clinical hemostasis problem in two of the four patients. In two patients who had replacements of 1.75 and 2.0 blood volumes, respectively, excessive clinical bleeding was still judged to be present following a platelet concentrate (table 4). Two units of FFP improved clinical

TABLE 1. Estimates of Percent of Original Platelet Count or Factor Levels Following 1 Blood Volume Replacement

	Percent of Original Level Following 1 Blood Volume Replacement*	95% Confidence Interval	Correlation Coefficient of Decline (r^2)
Platelet count	54	±8%	0.78
Fibrinogen	50	±12%	0.81
Factor V	57	±28%	0.74
Factor VIII	74	±38%	0.79
Factor IX	77	±18%	0.71

* Derived from regression analysis.

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TABLE 2. Coagulation Levels at the Time of Wound Closure in Patients Who Manifested No Clinical Bleeding during the Operative Procedure

Patient	Estimated Blood Loss (l)	Units of Packed Red Cells Concentrates Transfused	Crystalloid Administered (l)	Fraction of Blood Volume Replaced	Results of Coagulation Tests Measured at the Completion of the Study					
					PT/PTT (s)	Platelet Count (/mm³)	I† (mg/dl)	Factor Assays (%)		
								V	VIII	IX
Femur resection (50 kg female)	2.8	7	5.5	0.9	16/50*	257,000	103	20	78	43
Prostatocystectomy (68 kg male)	5.5	10	8.0	1.3	15/39*	108,000	165	46	55	175
Hemipelvectomy (118 kg male)	10.0	16	12.5	1.5	13/39*	141,000	108	55	140	77
Prostatocystectomy (72 kg male)	4.5	8	6.6	0.9	13/29	186,000	170	78	74	130
Prostatocystectomy (84 kg male)	3.8	5	7.4	0.7	13/30	150,000	200	90	83	98
Femur Resection (54 kg female)	3.0	7	5.5	0.7	15/36*	172,000	122	53	77	44
Liver Resection (76 kg male)	7.5	14	10.8	1.5	16/48*	129,000	112	21	131	44
Cystectomy (74 kg male)	3.8	6	6.0	0.8	13/28	219,000	160	75	169	104

* PT and aPTT abnormal at or prior to 1 blood volume replacement (normal PT = 10–13 s; normal PTT = 22–33 s).
† I = fibrogen.

TABLE 3. Coagulation Assessment at the Time Clinical Hemostasis was Judged Inadequate (Prior to Platelets)

	Packed Red Cell Units Transfused	Crystalloid Replaced (l)	Estimated Blood Volumes Replaced	Platelet Count (/mm³)	PT/PTT* (s)	I (mg/dl)	Factor Assays (%)		
							V	VIII	IX
Liver resection	11	6	1.3	69,000	16/44	117	47	105	45
Abdominal pregnancy†	16	9	1.75	38,000	38/150	40	11	20	24
Prostatectomy	16	10	1.9	62,000	16/47	120	36	78	69
Liver resection†	16	6	2.0	83,000	18/62	73	36	190	54

* Normal PT = 10–13 s; normal PTT = 22–33 s.
† A single donor platelet concentrate was administered, but clinical bleeding was still judged to be present.

TABLE 4. Clotting Studies of 2 Patients Who Received Both Platelets and FFP during the Study Period

	Blood Components	Observer Assessment of Hemostasis	Platelet Count (/mm³)	PT/PTT* (s)	I (mg/dl)	Factor Assays (%)		
						V	VIII	IX
Abdominal pregnancy	16 pRBC	Inadequate	33,000	38/>150	38	11	20	24
	20 pRBC + PC	Inadequate	84,000	36/>150	40	7	7	29
	22 pRBC + PC + 2 units FFP	Inadequate	NS	22/101	42	7	7	27
	24 pRBC + PC + 4 units FFP	Adequate	49,000	15/59	88	15	16	45
Liver resection	16 pRBC	Inadequate	84,000	18/62	73	36	190	54
	18 pRBC + PC	Inadequate	139,000	25/>150	60	27	86	49
	18 pRBC + PC + 2 units FFP	Adequate	133,000	18/60	115	NA	NA	NA

NA = not available; pRBC = packed red cells; PC = platelet concentrates.
* Normal PT = 10–13 s; normal PTT = 22–33 s.

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hemostasis in one patient; however, in the second patient following two units of FFP and a platelet concentrate, clinical hemostasis was still judged inadequate (table 4). An additional 2 units of FFP were administered after coagulation tests were sent for analysis. Hemostasis was judged adequate following the second 2 units of FFP (table 4). Specific clotting factor assays measured later in both patients revealed fibrinogen levels < 75 mg/dl and or Factor V and VIII levels less than 20% of normal prior to FFP (table 4). In the patient who received 4 units of FFP, Factor V and VIII levels were less than 10% prior to FFP. Clinical hemostasis was judged adequate following 4 units of FFP despite Factor V and VIII levels measured later of less than 20%. Three patients who received blood and fluid replacement for 1.3, 1.4, and 1.6 blood volume losses, respectively, required neither platelets nor FFP during the study period (table 2).

The study was terminated after hemostasis was achieved at the operative site and wound closure was started. None of the patients developed complications related to bleeding or hematoma formation in the postoperative period.

Discussion

In this study estimates of blood loss were made by the volume of blood in suction canisters and by assessing the saturation and number of laparotomy sponges. This measurement of blood loss is subject to significant intraobserver and interobserver variation. Overestimation or underestimation of the actual blood loss would change the estimates of blood volume replaced during the study.[8,10]

We measured coagulation factor levels and hematocrits at a time when blood volume, as judged by blood pressure, ventricular filling pressures (PAOP and/or CVP), and urine output, was similar to presurgical levels. Although relevant clinical assessments of vascular volume can be made using these measures, the use of ventricular filling pressures to assess blood volume is subject to significant errors.[9] Packed red cell concentrates and crystalloid solutions were used to replace blood and third space fluid loss.[8-10] The goal of packed red cell replacement was to maintain an adequate red cell mass, *i.e.*, hematocrit of 30. Crystalloid solutions were used to replace maintenance fluid and fluid losses. Although fluid replacement was guided by assessments of vascular volume, this replacement could have been either overestimated or underestimated, resulting in dilution or concentration, respectively, of the coagulation factor levels measured in the intravascular space. In summary, although vascular volume was maintained with packed red cell and crystalloid solutions according to clinically accepted monitoring methods, these methods could still result in significant quantitative and qualitative variations in blood volume that would influence the coagulation factor measurements.[8-10]

The quality of hemostasis was assessed by the same anesthesiologist (D.J.M.) who also managed blood and fluid therapy in all patients with confirmation by the attending surgeon (12 different surgeons with 12 patients). An important bias could have been introduced by this method, because the anesthesiologist was aware of prior blood and fluid therapy and different surgeons assisted in the decision. Assessment of the quality of hemostasis requires repetitive evaluations of the operative field by an observer. We consider that blinding an observer to the intraoperative management and in particular to blood and fluid replacement therapy was not desirable or possible in this study.

The decision to use component therapy in the form of platelets or FFP was based on the platelet count—the only laboratory assessment of hemostasis rapidly available to the anesthesiologist (within 30–40 min of collection). The fibrinogen level, PT, aPTT, and coagulation factor levels were not available to guide therapy in a timely manner following the assessment of increased clinical bleeding.

There were significant abnormalities of the two most common coagulation tests used to assess coagulation, the PT and aPTT, prior to 1 blood volume replacement in nine of the 12 patients despite the absence of clinical bleeding. This study appears to add to the findings of retrospective studies that suggest that preoperative abnormalities in PT and aPTT are poor indicators of risk of bleeding during operation in patients with no history of bleeding.[13-15] In clinical studies of traumatized patients who required massive transfusion, an elevated PT and PTT also did not correlate with increased bleeding.[16-22]

The sensitivity of the PT and aPTT to actual levels of coagulation factors varies with the measurement technique used and the specific clotting factor deficiency that exists.[16,23,24] Correlation of the degree of PT or aPTT abnormality with coagulation factor levels has been determined for a variety of measurement methods.[16,23,24] The PT and aPTT are expected to become elevated above normal when levels of Factor V, Factor VIII, and Factor IX are less than 50% of values found in a control patient population.[24]

In 1961 Aggeler reviewed clinical experiences with surgical management of patients with isolated coagulation factor deficits.[25] In patients who had only a single clotting factor deficiency, coagulation factor levels 20–30% of normal were apparently adequate to prevent bleeding problems during surgery. In trauma patients when massive blood loss was replaced with modified whole blood, fibrinogen levels of less than 80 mg/dl, and Factor V and VIII levels of ≤30% were cited as indications for coag-

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ulation factor replacement.[16,17] Our study may agree with these findings as in ten of 12 patients who received multiple red cell transfusions increased clinical bleeding did not occur if the platelet count was adequate and in addition, if fibrinogen levels of greater than 75 mg/dl and clotting factor levels of more than 20% were present. This may explain why a mildly elevated PT and/or aPTT (expected findings when coagulation factor levels are less than 50% of normal values) did not result in increased clinical bleeding. In the two patients who had continued bleeding despite platelet concentrates, fibrinogen levels were less than 75 mg/dl, Factor V or Factor VIII levels were less than 20% of normal, and the PT and aPTT in these two patients was prolonged to 1.5 times control values. In other patients who did not require coagulation factor replacement, fibrinogen levels were greater than 100 mg/dl and coagulation factor levels were more than 20% of control values. In this small prospective study fibrinogen levels less than 75 mg/dl and PT and aPTT levels greater than 1.5 times control values might represent the minimum effective levels required for clinical hemostasis during surgery. A larger clinical study is required to assess the minimum effective coagulation factor level required for clinical hemostasis and address the specific role of FFP in coagulation factor replacement during packed red cell replacement of major blood loss.

In prior studies of coagulation during major blood loss,[16-21] platelets were judged the most important component to treat clinical bleeding. In these studies of trauma patients in whom massive blood loss was replaced with modified whole blood (platelets and cryoprecipitate removed) or whole blood, the correlation was poor between the number of units transfused and clotting factor levels. This suggests that consumption of coagulation factors was a more significant problem than dilution. Coagulation factor activity in the modified whole blood used to replace blood loss[16,17,19] and coagulation factor consumption that might result from hypotension and trauma in patients who require emergency surgery might be expected to influence coagulation factor measurements more than in our study of patients who, during elective surgery, had major blood loss replaced with Adsol packed red cell concentrates and crystalloid solutions. Although decreases in all the coagulation factor levels were expected on the basis of dilution, the factor levels we measured were greater than anticipated. Factor VIII levels varied considerably (95% confidence interval, ±38%) (fig. 4; table 1), and even after the replacement of 1 blood volume Factor VIII activity was still estimated to be 74% of original levels (table 1). This variability in Factor VIII levels is probably consistent with storage in endothelial cells and release from the endothelium during surgical stress.[26] Similar to other studies, the platelet levels measured were also greater than expected on the basis of dilution alone.[20] A variable degree of platelet and coagulation factor storage and release might explain the higher than anticipated levels of platelets, Factor IX, Factor V, and fibrinogen levels.

Platelet transfusions in prior studies were judged the most important component in the initial management of the patient bleeding during surgery for trauma.[18-21] When a coexistent thrombocytopenia or qualitative abnormality of platelet function exists or develops during an operative procedure, it is difficult to address the minimum coagulation factor levels required for hemostasis until the thrombocytopenia or platelet function abnormality is corrected.[16,17] For this reason a platelet concentrate obtained by pheresis of a single donor was transfused to patients who were judged by two (perhaps biased) observers (the anesthesiologist and attending surgeon) to be bleeding, but not until confirmation that platelet counts were indeed less than 100,000. If after platelets clinical bleeding persisted, FFP was administered. Unlike prior studies using modified whole blood in trauma patients,[16,17] we found that when packed red cell concentrates were used to replace blood loss during elective surgery, a significant correlation existed between blood volume replaced and decreases in fibrinogen, Factor V, Factor VIII, and Factor IX levels. In addition, decreases in fibrinogen levels during Adsol packed cell replacement were a guide to significant declines in the other coagulation factor levels we measured (V, VIII, and IX).

Clinical assessments of coagulation during the operation combined with laboratory confirmation of coagulation in the form of platelet counts, PT, aPTT, and fibrinogen levels are at present the best indications of the need for either platelet concentrates or FFP in situations of major blood loss. PT and aPTT levels of 1.5 × control levels and fibrinogen levels of less than 75 mg/dl were associated with a clinical assessment of the need for FFP in the two patients who received FFP in addition to platelets during Adsol packed red cell replacement of major blood loss. This situation did not occur in any of the patients in this study until more than 1.0 blood volume had been replaced with packed red cell concentrates and crystalloid. Our study indicates that the PT and aPTT, although perhaps guides to coagulation factor levels, probably can become distinctly abnormal without an absolute requirement for coagulation factor replacement.

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