Coagulation Defects Associated with Massive Blood Transfusions

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A BLEEDING diathesis has been frequently described in patients receiving multiple transfusions of stored blood but agreement is lacking regarding its pathogenesis and treatment [16, 39, 42] Acquired dilutional thrombocytopenia,[15, 25, 27, 30] loss of labile coagulation Factors V and VIII,[32, 33] fibrinolysis,[37, 44] and disseminated intravascular coagulation [35] have been suggested as the causes of coagulation defects associated with massive blood transfusions.

The lack of agreement may reflect in part the difficulty of systematically studying these often seriously ill patients and separating the effects of transfusion from other factors which may affect coagulation and hemostasis. We studied the effects of rapid, multiple transfusions in acutely traumatized, presumably previously healthy battle casualties which should in part eliminate other complicating coagulopathies associated with many chronic diseases. The results of this study suggest a quantitative platelet deficiency as the cause of excessive bleeding associated with massive transfusions.

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Materials and Methods

Studies were performed on 21 battle casualties who were admitted to the U. S. Naval Support Activity Hospital, DaNang, Republic of Vietnam and whose clinical condition suggested that more than ten units of blood replacement would be required. All blood administered was collected in the United States in Fenwal plastic bags containing 70 ml. acid-citrate-dextrose (ACD) solution A and subsequently shipped to Vietnam. At the time of transfusion, the age of the blood was between eight and 20 days. A standard major and minor match in albumin after 15 minutes incubation followed by indirect Coombs testing of the saline washed cells was performed on all units prior to administration.

Coagulation studies were performed immediately upon admission of the patient to the triage which was usually within 1 to 2 hours from the time of wounding. Fluid

administration was guided by blood pressure, pulse, central venous pressure, and urinary output. Arterial blood gas measurements were made every 2 hours or more often to evaluate the adequacy of pulmonary ventilation and the need for sodium bicarbonate therapy. Most units of blood were warmed in a heating coil to 37° C. prior to administration.

Blood for the coagulation studies was drawn from a plastic catheter inserted into the inferior vena cava via a femoral vein cutdown, taking care to thoroughly irrigate the catheter with blood prior to taking samples. Blood was drawn into a plastic syringe, immediately placed in the appropriate anticoagulant, and mixed thoroughly. Occasional samples were taken from a clean direct venepuncture utilizing a "two syringe technic."

Coagulation Methods

The prothrombin time (PT) was determined by the one stage method of Quick on citrated plasma (0.5 ml. 3.8% sodium citrate and 4.5 ml. venous blood) utilizing the Fibrometer system and simplastin as the tissue thromboplastin[28]; all tests were run in conjunction with normal control samples (Normal values: 13.8 ± 1.4 [± 2 S.D.]). The Partial Thromboplastin Time (PTT) was determined on citrated plasma by using activated platelin with celite in a fibrometer system (0.5 ml. 3.8% sodium citrate and 4.5 ml. venous blood)[28]; all tests were performed in conjunction with normal control plasma samples (Normal values: 40.8 ± 8.48 [± 2 S.D.]). Platelet counts were performed on venous blood collected in dipotassium versinate (1 mg. powder/ml. blood) by the standard method of Brecher and Cronkite[28]; all counts were performed in duplicate. (Normal values for this laboratory: 140,000 – 440,000/mm.^{3}). Prothrombin Consumption Time (PCT) was performed by the method of Quick utilizing simplastin as the tissue thromboplastin and Ba SO_4 absorbed plasma as the substrate[28]; (Normal value for this laboratory > 21 seconds). The bleeding time was performed by the standard method of Ivy.[28] Clot retraction was determined by incubating blood samples at 37° C. and observing for per cent clot retraction at 24 hours. The above tests were performed prior to replacement of blood and every five units thereafter.

The euglobulin lysis time was performed on citrated plasma (0.5 ml. 3.8% sodium citrate and 4.5 ml. venous blood) by the method of van Kaulla and Schultz.[28] (Normal values for this laboratory: > 2 hours.) The presence of Fibrin Split Products was determined by using a standard immunodiffusion method in agar gel employing specific rabbit antiserum against human fibrinogen.[10] EACA was not added to the blood after collection. In patients 9 through 20, the presence of fibrin split products and in patients 12 through 20 eugobulin lysis times were detemined immediately before and after every 15 units of blood administered.

In patients 3, 5, 7, 9, and 21 the above tests were performed immediately prior to, 15 minutes and 60 minutes after administration of 500–1,000 ml. of fresh frozen plasma (FFP). In patients 7, 8, 14 and 21 these tests were performed immediately prior to, 15 minutes and 60 minutes after the administration of 1,500 to 2,000 ml. of fresh blood (no older than 3 hours). All patients were evaluated clinically by physicians without knowledge of results of laboratory tests throughout operation for evidence of increased oozing into the surgical field, bleeding from the catheter sites, and appearance of petechiae and ecchymosis.

Results

Significant clinical coagulation defects occurred when 20 to 25 units of blood had been administered (Table 1). Only one patient developed a bleeding tendency before 20 units of blood had been given while

TABLE 1. *Correlation Between Units of Blood Received and Incidence of a Bleeding Tendency in Patients Receiving ACD Stored Blood*

Units of Blood Received	No. of Patients Studied	No. of Patients with a Bleeding Tendency	%
0	21	0	0
5	21	0	0
10	21	0	0
15	19	0	0
20	14	4*	23
25	11	6	55
30	7	7	100

* Bleeding was observed in one patient after 18 units of blood.

all patients exhibited bleeding tendencies when 30 units of blood had been given. All blood was administered within a 5-hour period. The rate of ACD blood administration ranged from 1,200 cc. to 7,500 cc. per hour and did not correlate with the incidence of clinical bleeding tendencies. Of nine patients who did not develop a bleeding tendency eight survived. Of 12 patients who developed a bleeding tendency, four died. Three died after 3 to 4 hours of operating time and one died 4 days postoperatively.

Although the PCT remained essentially normal during multiple blood transfusions, the PTT and PT became abnormally elevated when 15 units of blood had been administered (Fig. 1). Examination of the PTT and PT values of individual patients reveals no pattern of developing abnormality associated with clinical bleeding (Table 2). In fact the PTT and PT actually improved or remained unchanged as oozing developed in three of the eight patients studied. Furthermore, a return of the PTT and PT to normal by administration of fresh frozen plasma did not alter the bleeding tendency in five patients (Table 3).

All patients exhibited a bleeding diathesis when platelet counts fell below 60,000/mm.^{3} (Table 2). When the mean decrease in platelets was compared to the predicted level of decline for a person with an initial platelet count of 240,000/mm.^{3} and a blood volume of five liters receiving platelet free blood, the curves were practically parallel (Fig. 2). The predicted platelet counts were determined using the formula:

$$(\text{Platelet})_t = (\text{Platelet})_o\, e - \frac{\text{volume out}}{\text{total volume}}$$

In four patients with clinical coagulation defects, administration of three to four units of fresh blood resulted in marked increases in platelet counts and a subsequent cessation of bleeding (Table 4).

Euglobulin lysis times were abnormal in four of nine patients at the time of admission, but returned to normal in all cases by the time 20 units of blood had been administered. Fibrin split products were present only in patient number 16 which will be discussed. Since blood was not collected in epsilon amino caproic acid, this may reflect a false positive result from the increased fibrinolysin in this case.[9]

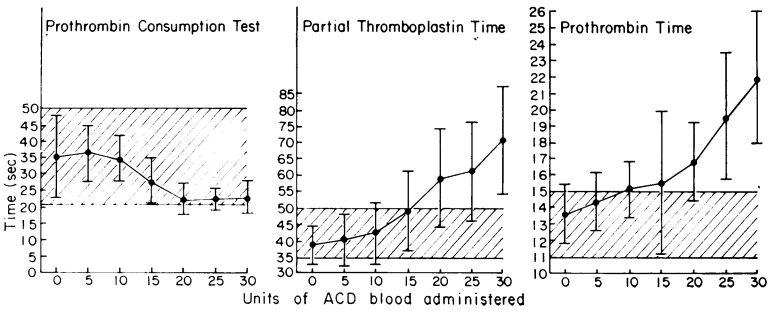

FIG. 1. Correlation between units of ACD stored blood on the prothrombin consumption test, partial thromboplastin time, and prothrombin time. The brackets represent one standard deviation. The shaded areas represent the area of normal limits in our laboratory.

TABLE 2. *Comparison of Platelets, Prothrombin Time, and Partial Thromboplastin Time Immediately Before and After Appearance of a Clinical Bleeding Tendency*

	Last Value Measured Before Bleeding			First Value Measured after Bleeding Began		
Patient	Platelet (1,000/mm.³)	PT* (sec.)	PTT** (sec.)	Platelet (1,000/mm.³)	PT (sec.)	PTT (sec.)
1	85	20.0	86.5	59	20.9	98.4
3	75	16.6	59.9	55	16.8	65.5
5	72	16.8	54.9	50	15.9	57.8
6	93	12.8	53.6	58	13.4	54.4
7	90	Received FFP		55		
8	70	20.4	53.2	45	20.8	55.0
14	82	19.1	67.9	52	20.4	60.4
17	75	18.9	63.9	45	19.0	66.9
18	73	18.4	62.4	51	17.2	56.9
19	61	16.9	46.4	52	16.9	43.4
21	117	15.9	54.4	58	17.1	53.6
Mean	81	17.6	60.3	53	17.8	61.2

* Prothrombin time.
** Partial thromboplastin time.

The Ivy bleeding time and clot retraction were abnormal when five units of blood had been administered which was well before evidence of clinical bleeding appeared. Thus no correlation between these tests and bleeding tendencies was found. Except for being listed in Table 1, patient 16 was excluded from the study. Upon admission he had fibrinolysis and possibly disseminated intravascular coagulation by laboratory tests. This became clinically evident intra and postoperatively. The bleeding tendency was treated successfully with heparin, but since the patient had a bleeding tendency before receiving stored blood, it seemed reasonable to exclude him from the study.

Discussion

Results of this study indicate that significant bleeding tendencies occur after 20 to 25 units of ACD stored whole blood have been transfused. A dilutional quantitative defect in platelets appears to be the main cause for bleeding and this condition can be treated successfully with fresh blood. This finding is not surprising in view of the severe damage to platelets that occurs when blood is stored at 4° C.[29] Although platelets normally decrease gradually in ACD blood, considerable thromboplastic activity is retained up to 21 days' storage.[19, 36] Platelets disappear from the circulation, however, almost immediately after infusion.[4] Further evidence for a dilu-

TABLE 3. *The Effect of Fresh Frozen Plasma (FFP on Coagulation Tests of Five Patients with Clinical Bleeding Tendency*

Time of (FFP) Administration	Platelets (1,000/cu. mm.)	Prothrombin Time (sec.)	Partial Thromboplastin Time (sec.)	Prothrombin Consumption Test (sec.)
Pre FFP administration	54 ± 17	16.3 ± 3.5	59 ± 11	29 ± 7
15 min post FFP administration	53 ± 11	14.1 ± 2.8	52 ± 6	28 ± 7
60 min post FFP administration	54 ± 20	13.7 ± 2.5	41 ± 10	26 ± 7

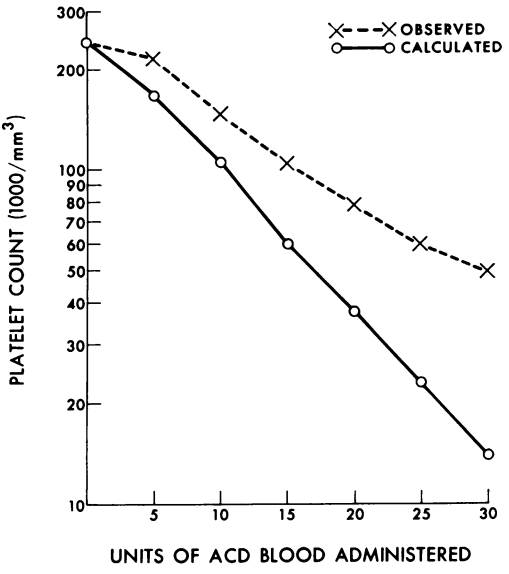

FIG. 2. Comparison between mean observed platelet counts with multiple tranfusion of ACD stored blood and platelet count (predicted) in a person receiving platelet free blood. The predicted platelet counts were calculated with the following equation:

$$(\text{Platelet})_t = (\text{Platelet})_o\, e^{-\frac{\text{volume out}}{\text{total volume}}}$$

tional cause of thrombocytopenia is that the observed mean platelet counts parallel the predicted platelet counts based on a standard washout equation (Fig. 2). That observed platelet counts were slightly greater than the predicted platelet counts might be explained by blood volumes being different from the 5 liter blood volume used to calculate predicted counts. Another explanation may be that as platelet count falls, bone marrow is stimulated to increase its megakaryocytic mass and thus platelet production. We felt the close approximation of a mathematically derived curve with results obtained from clinical patients with many variables supported the concept of thrombocytopenia from a dilutional etiology.

Normal PCT in the presence of bleeding tendencies suggests that the remaining platelets were functioning adequately and a gross qualitative platelet defect was not present.[14] Although PCT is dependent on a number of factors, a normal value indicates that platelet factor 3 is being released normally.[26] Other qualitative defects of platelet function such as aggregation and adhesion are possible in the presence of a normal PCT; thus, a qualitative defect in platelets has not been ruled out completely by this study.[5]

When thrombocytopenia reaches levels of approximately 65,000/mm.³, a bleeding diathesis usually occurs. However, several authors caution against the concept of an absolute threshold for platelets, particularly in the presence of varying hemostatic challenges.[17, 18] Winchell suggests that a disruption of vascular integrity must accompany thrombocytopenia to produce bleeding as evidenced by no hemorrhage in otherwise healthy dogs suddenly depleted of platelets.[43] Reports concerning the number of platelets required to provide hemostasis in traumatic or surgical wounds vary from platelet counts of 50,000 to 75,000 mm.³,[2, 3, 11, 12] which is consistent with our results, to platelet counts greater than 100,000 mm.³ [34, 40]

Other reports indicate that even with massive transfusions, platelet counts do not decrease to levels which may cause bleeding.[11, 20] In the study of Gollub *et al.*,[20] fresh blood was used in addition to stored blood. A recent study on Vietnam causalties indicated that platelet counts leveled off at 100,000 mm.³ after 12 units of blood had been given and rarely decreased further.[11] This was not the case in our study. Since the platelet storage pool is relatively small,[22] platelet counts may potentially fall to levels which were found in our patients.

In addition to platelets, stored bank blood becomes depleted in proaccelerin (Factor V) and AHG (Factor VIII). Horowitz suggested that PTA (Factor XI) may also be depleted.[23] Thus, another interpretation of our data is that both thrombocytopenia and loss of labile Factors V and VIII were causes of bleeding which

TABLE 4. *The Effect of Fresh Blood (FB) on Coagulation Tests of Four Patients With Clinical Bleeding Tendency*

Time of FB Administration	Platelets (1,000/cu. mm.)	Prothrombin Time (sec.)	Partial Thromboplastin Time (sec.)	Prothrombin Consumption Time (sec.)
Pre-FB administration	50 ± 16	19.3 ± 3.1	58 ± 16	29 ± 17
15 min post FB administration	108 ± 26	16.8 ± 5.2	59 ± 18	33 ± 10
60 min post FB administration	151 ± 32	17.1 ± 4.7	53 ± 12	39 ± 13

followed multiple transfusions of ACD blood. Administration of FFP only supplied Factors V and VIII while fresh blood supplied all Factors plus platelets. We may have been able to determine whether thrombocytopenia was the only cause of bleeding by administering platelet concentrates. This was not done for technical and clinical reasons. Although our data cannot refute the above conclusion, the following reasons suggest loss of Factors V and VIII to be secondary to thrombocytopenia as the cause of a hemorrhage diathesis following massive blood transfusions. The PTT (which measures all Factors except VII, XIII, and platelets) and PT (which measures I, II, V, VII, and X) were abnormally elevated, but did not correlate with clinical bleeding. Factors V and VIII are depressed 20 to 50% of normal in blood which has been stored for three weeks.[8, 19, 31] However, Factor V levels only 5 to 25% of normal are required for hemostasis in patients undergoing major operations.[7, 41] Adequate surgical hemostasis require that Factor VIII be at least 30% of normal.[2] Thus, while expected levels of depletion of these factors are severe enough to cause prolongation of the PTT and PT which we observed,[13, 21] it is highly unlikely that they would result in excessive bleeding during massive transfusion before the effects of thrombocytopenia occur. Further supporting evidence is the finding that although the PTT and PT return to normal with FFP administration, bleeding tendencies persisted.

Previous studies on traumatized patients and experimental animals demonstrated the development of a hypercoagulable state followed by rapid development of disseminated intravascular coagulation characterized by a loss of Factors V, VIII, and platelets even without transfusion of stored blood.[1, 6, 24] Absence of fibrin split products in all but one patient and normal euglobulin lysis times in all patients receiving 20 or more units of blood suggests the absence of disseminated intravascular coagulation or primary fibrinolysis. Although more sensitive methods than used in this study are available for detection of fibrin split products,[38] permanent cessation of the bleeding tendencies with fresh blood,[1, 6, 24] the absence of significant coagulopathy prior to the initiation of transfusion, and the close approximation of our findings to theoretical predictions of dilutional platelet, loss do not support the possibility of significant intravascular consumption of platelets as a cause of the observed thrombocytopenia and subsequent oozing.

Two previous studies are pertinent. Krevans and Jackson found a bleeding tendency in only one of 15 patients all of whom received 15 units of blood or less.[25, 27] This patient was a 75-year-old woman who developed a platelet count of 44,000/mm.^{3} after receiving 11 units of stored blood. However, ten of 11 patients who received over 15 units bled abnormally. Patients in both groups who bled abnormally, had platelet counts below 65,000/mm.^{3}; in the nonbleeders, a low platelet count was present in only two (56,000 and 38,000/mm.,^{3} respectively). Stefanini *et al.* studied 70 patients who received five or more transfusions during

operation.[35] Twenty-four developed overt bleeding after receiving eight to 29 units of blood. Only four began oozing after receiving 11 units. Most patients were severely thrombocytopenic at the time of bleeding except for four patients who had platelet levels between 90,000/mm.^{3} and 105,000/mm.^{3} Virtually all patients who bled excessively demonstrated an abnormal fibrinolysin. However, its incidence in nonbleeders was not stated. These reports are consistent with the findings in this study. Transfusion of large amounts of platelet deficient stores blood resulted in a progressive platelet depletion with eventual bleeding when the platelet count fell below 65,000/mm.^{3} This condition can be successfully treated with fresh blood.

Summary and Conclusions

Studies of blood coagulation parameters were carried out in 21 combat casualties who received a large number of transfusions of stored blood anticoagulated with acid-citrate-dextrose solution. Twelve patients, all of whom developed thrombocytopenia with platelet counts less than 60,000 per cubic millimeter, developed hemorrhagic diatheses. Although fresh frozen plasma was not a successful form of treatment, bleeding tendencies ceased when fresh blood was infused. It is concluded that although several factors may be involved, dilutional thrombocytopenia due to replacement of blood loss with stored blood is the primary cause of bleeding which follows massive blood transfusions.

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