Hemostasis in Massively Transfused Trauma Patients

R. B. COUNTS, C. HAISCH, T. L. SIMON, N. G. MAXWELL, D. M. HEIMBACH, C. J. CARRICO

From the Puget Sound Blood Center, and the Departments of Medicine and Surgery, University of Washington, Seattle, Washington

Twenty-seven patients requiring massive transfusions were studied prospectively to determine whether administration of stored, modified whole blood induced a primary disorder of hemostasis evidenced by generalized microvascular oozing. Platelet counts fell in proportion to the number of units of blood transfused. In contrast, the levels of factors V and VIII correlated poorly with the units of blood transfused, 85% of the total variation in the levels being due to influences other than transfused blood. Levels of all other clotting factors were unrelated to the number of units of blood given. Eight patients developed abnormal bleeding. The cause appeared to be dilutional thrombocytopenia in five patients, and DIC in three. In six of the eight, bleeding was controlled with platelet concentrates alone. Two patients were given cryoprecipitate also. The most useful laboratory test for predicting abnormal bleeding was the platelet count. Fibrinogen levels should be followed as an aid in the diagnosis of DIC. The BT, PT, and PTT were not helpful in assessing the cause of bleeding, unless they were greater than 1.5 times the control value. We recommend that any patient receiving massive transfusions who develops diffuse microvascular bleeding be given platelet concentrates. Platelet counts as high as 100,000 may be required to control bleeding from surgical woulds. It is not necessary to supplement transfusions of stored, modified whole blood with fresh blood or fresh frozen plasma.

A MAJOR CHANGE IN COMMUNITY blood banking practice in the last ten years has been the widespread adoption of blood fractionation and specific component transfusion which allows the provision of platelets, cryoprecipitate and albumin for patients with special needs for these components.

In many communities, red cells are used almost exclusively for transfusion. These are supplemented with albumin or other volume expanders and with plasma if necessary. The use of red cells and albumin for transfusion to patients who are bleeding is inefficient since approximately 450 ml of plasma must be processed to yield one 250 ml bottle of 5% albumin. A more efficient fractionation scheme consists of the salvage of both platelet concentrates and cryoprecipitate from a unit of whole blood using a triple-bag system. The supernatant plasma after cryoprecipitate removal is returned to the red cells to provide "modified whole blood" which differs from whole blood in having had 85% of the platelets, 60% of the factor VIII and about 25% of the fibrinogen removed.[19] The Puget Sound Blood Program provides modified whole blood for bleeding patients, who need, simultaneously, both red cells and plasma volume replacement.

Concerns about depletion of platelets and coagulation factors in patients who receive large volumes of blood within a short time have led to recommendations that transfusion of stored or modified whole blood be supplemented with "fresh warm blood" from walking donors.[8,15] Others have suggested that fresh blood or fresh frozen plasma is necessary, when large volumes of stored blood are transfused, in order to provide coagulation factors.[1,22] We have examined the hypothesis that transfusion of modified whole blood leads to a primary defect in hemostasis because of depletion of platelets of clotting factors. Our results demonstrate that transfusion of large volumes of modified whole blood does lead to dilutional thrombocytopenia but does not cause clinically significant coagulation factor deficiencies. These findings have important implications for both the clinical management of massively bleeding patients and the management of community blood resources in this country.

Procedures

Patients

The study group consisted of 27 patients who sustained major trauma, massive GI hemorrhage, or aortic aneurysm rupture and who were admitted to the Trauma Center at Harborview Medical Center with systolic blood pressure less than 80 mmHg. The patients ranged in age from 18 to 80. Whole blood was drawn from healthy random donors at the Puget Sound Blood Center

Reprint requests: Dr. R. B. Counts, Puget Sound Blood Center, Terry and Madison Streets, Seattle, Washington 98104.

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into CPD anticoagulant and stored at 2–6° according to standard procedures.

Platelet concentrates were produced according to the method of Slichter and Harker.[20]

Cryoprecipitated AHF was prepared by the method reported by Slichter et al.[19] using a refrigerated freezing-thawing bath (Forma Scientific, Marietta, Ohio) that allows the cryoprecipitate to be removed and modified whole blood to be available for transfusion within eight hours of the time the blood was collected.

Platelet counts were performed in duplicate using an electronic particle counter.[2]

Blood for coagulation screening tests and clotting factor assays was collected by venipuncture into plastic tubes. It was anticoagulated with 1/10 volume of 3.8% sodium citrate with appropriate adjustment for hematocrit if the patient was anemic. Samples were spun at 4500 × *g* for 30 minutes to remove platelets. The platelet-poor plasma was frozen at −70° until assays were performed.

Tests of coagulation were done by standard methods: the prothrombin time (PT) by the method of Quick using human brain thromboplastin,[13] the partial thromboplastin time (PTT) by the method of Proctor and Rapaport.[12] Fibrinogen was measured as total clottable protein.

Factors V, VII, X and prothrombin were assayed by a one-stage test based on the prothrombin time using human brain thromboplastin. Factors VIII, IX, and XI were determined by one-stage PTT-type assays[7] using human brain cephalin. Normal plasma for coagulation standards was a pool of plasmas from 30 healthy random donors. Plasmas deficient in factor VIII or factor IX were obtained by plasmapheresis of patients with severe hemophilia A or B. Plasma deficient in factor V was aged, oxalated plasma. Plasmas deficient in factors II, VII, X, or XI were purchased from George King Biomedical, Salem, New Hampshire. Bleeding times (BT) were determined by the Ivy template method.[6]

Assays of Clotting Factors in Stored Blood

Ten units each of whole blood, modified whole blood (platelets removed) and modified whole blood (cryoprecipitate removed) and eight units of modified whole blood, (both platelets and cryoprecipitate removed) were stored in a blood bank refrigerator at 2–6°. Samples for assays were removed by an aseptic technique, at the time the blood was collected (zero time), and at one to five day intervals over a period of 21 days. Duplicate assays were performed on each sample for clotting factors II, V, VII, VIII, IX, X, XI and fibrinogen.

Patient Studies

All patients were initially resuscitated by emergency paramedics ("Medic One", Seattle Fire Department) using only Ringer's Lactate solutions for blood volume expansion. Initial blood samples were obtained at Harborview Medical Center immediately upon entering a patient in the study. Subsequently, samples were obtained at approximately 12 hour intervals for 96 hours, or more frequently if the patient was felt clinically to have abnormal bleeding. Bleeding caused by a primary disorder of hemostasis was distinguished from "surgical bleeding" by two criteria. 1) It involved diffuse microvascular oozing rather than rapid bleeding from an identifiable lesion. 2) It was manifested by bleeding from multiple areas such as wound skin margins and venipuncture sites in addition to the operative site itself.

We attempted in each case to obtain the initial blood sample before the patient received any blood components. Transfusion of blood components was guided by the clinical judgement of the attending surgeons. Platelet concentrates, plasma or cryoprecipitate were given only when there was abnormal, microvascular bleeding and laboratory evidence of a platelet or coagulation factor deficiency. Screening tests (thrombin time, prothrombin time and PTT), platelet counts, and specific assays for each of the clotting factors were performed on all samples drawn for this study.

Analysis of Data

Standard statistical methods were used for data analysis. Regression lines were calculated by the least-squares method and correlations estimated by calculation of the coefficient of determination r^2.[4] Analysis of variance was used to calculate variance ratios, distributed as F, to test the significance of regression.[3]

Results

Clotting Factors in Stored Blood

The only clotting factors which deteriorated significantly on storage were factors V and VIII (Fig. 1). There was no difference between the rate of disappearance of factor V activity from modified whole blood and the rate of disappearance from whole blood from which either cryoprecipitate or platelets or both had been removed, *i.e.*, the regression lines for whole blood, cryoprecipitate-poor blood, platelet-poor blood, and cryoprecipitate-poor-platelet-poor blood were identical. The disappearance of factor V appeared, surprisingly, to be linear with time, zero-order in factor V concen-

tration. Factor V levels remained above 50% of normal for at least 14 days of storage at 4°. The mean factor V level at 21 days was 35 ± 7% (1 S.D.) of the starting level.

The mean level of residual factor VIII activity in modified whole blood following cryoprecipitate removal was 15%. Figure 1 shows the disappearance of factor VIII in platelet-poor modified whole blood. The initial decay of factor VIII activity had a $t_{1/2}$ of about 24 hours for the first two days. By 48 hours the activity had decreased to 30% of the initial activity, approximately the minimum level necessary for hemostasis. The mean levels of other factors in whole blood and modified whole blood after 21 days of storage are given in Table 1. Except for factors VIII and V, all factor levels were higher than 57% of the original blood level after 21 days of storage.

Clinical Studies

During the study, 893 units of blood were administered to the 27 patients, a mean of 33 units per patient, the range was from 8–65 units. Of this total, 621 units (69%) were administered within the first 24 hours of hospitalization, 114 units (13%) between days one to five and 158 units (18%) later.

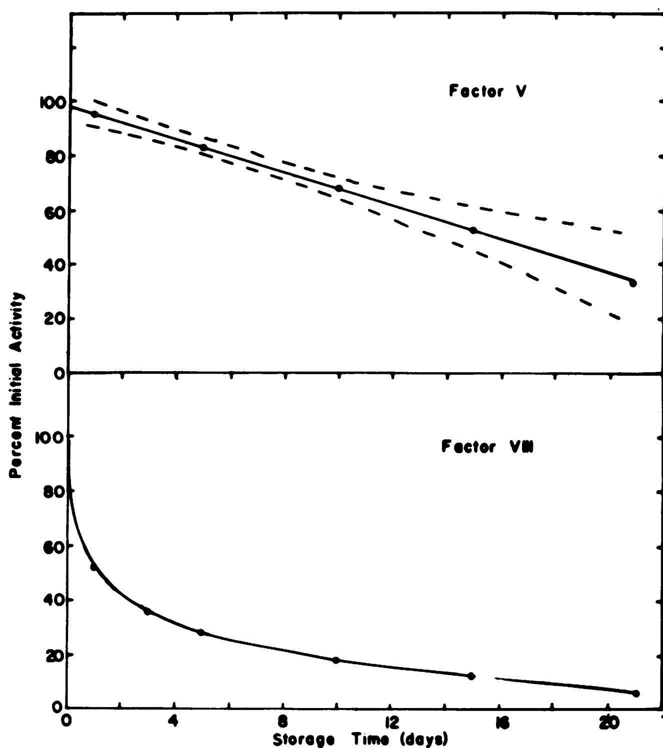

FIG. 1. Levels of factors V (above) and VIII (below) in CPD-anticoagulated blood stored at 4°. Least squares regression lines for factor V calculated from assays of ten units of blood from normal, random donors. The 95% confidence limits are given for factor V. For factor VIII the initial half-time is 24 hours.

TABLE 1. *Clotting Factor Levels in Modified Whole Blood (CPD Anticoagulant) Stored at 4°*

Clotting Factor	Level After Storage (Days) as a Percentage of the Initial Level: 14 Days	21 Days
Prothrombin	87	70
VII	57	66
IX	106	97
X	90	85
XI	99	107
XII	133	117
Fibrinogen	98	109

Only nine units (1%) of blood were administered within 24 hours of the time they were collected. Four hundred seventy-nine units (59%) were one to five days old at the time of transfusion; 202 units (23%) were six to ten days old and 191 units (21%) were 11–21 days old. Thus, about half the blood was less than five days old when it was transfused, and 75% was less than 10 days old.

The kinds of blood components transfused are listed in Table 2. Only 5 of 893 units were unprocessed whole blood. Eighty-three per cent of the blood transfused was modified whole blood which had either platelets or cryoprecipitate, or both, removed. Almost half the units transfused (419 units—47%) had had cryoprecipitate removed.

Platelets

To analyze the effect of transfusion of blood on the platelet count, platelet counts were plotted against the number of units of blood which the patient had received up to the time the sample was obtained for the platelet count (Fig. 2). Each point on the graph represents a platelet count obtained prior to the transfusion of any platelets. There was a strong relationship

TABLE 2. *Types of 893 Units of Blood Distributed by Blood Center and Administered to 27 Patients*

	Number	
1. Cryo-poor whole blood	170	19
2. Platelet-poor whole blood	326	36
3. Cryo and platelet-poor whole blood	249	28
4. Whole blood	5	1
5. Red blood cells	122	14
6. Unidentified	21	2
Total	893	100

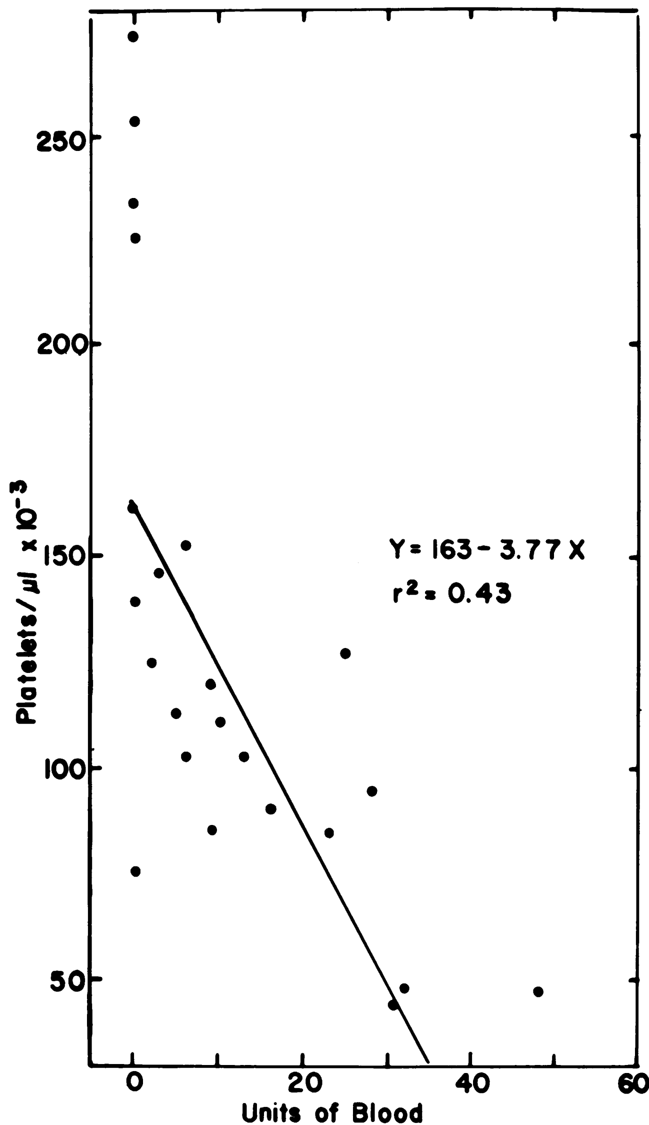

FIG. 2. Plot of platelet counts against the number of units of blood transfused to the patient prior to the time the sample was obtained for the platelet counts. No platelet transfusions had been given to any of the patients represented in this graph.

between thrombocytopenia and the number of units of blood transfused up to the time the platelet count was done. The regression was highly significant (F = 25.7; 1, 34 D.F.; $p = 1 \times 10^{-5}$). There was considerable variation in the platelet levels, however, the coefficient of determination, r^2, was 0.43.

Factors V and VIII

The levels of factors V and VIII tended to be lower in patients who had received a large amount of blood than in patients who had received no blood (Figs. 3 and 4). In each case, the slope of the least squares regression line was significantly different from zero as estimated by the analysis of variance; but the coefficient of determination for each line was less than 0.2.

Factor VII

Figure 5 is a scatter diagram of factor VII levels against the number of units transfused up to the time the sample was drawn. The correlation is poor ($r^2 = 0.09$), the regression is not statistically significant (P = 0.07). The total variance in factor VII levels was large. It was not possible to predict the level in a given patient from the units of blood he had received.

Fibrinogen

Fibrinogen level as a function of units of blood received by the patient is plotted in Figure 6. There is no correlation between the two variables. The results of similar analysis of factors X, XI, and XII were similar to fibrinogen. The levels of each of these factors appeared to be completely unrelated to the number of units of blood transfused.

Clinical Course of Patients

Nineteen of the 27 patients studied had no abnormal bleeding. Eight had a primary hemostasis abnormality within 48 hours of admission, manifested by uncontrolled oozing at multiple sites (such as skin margins and venipuncture sites) in addition to the surgical

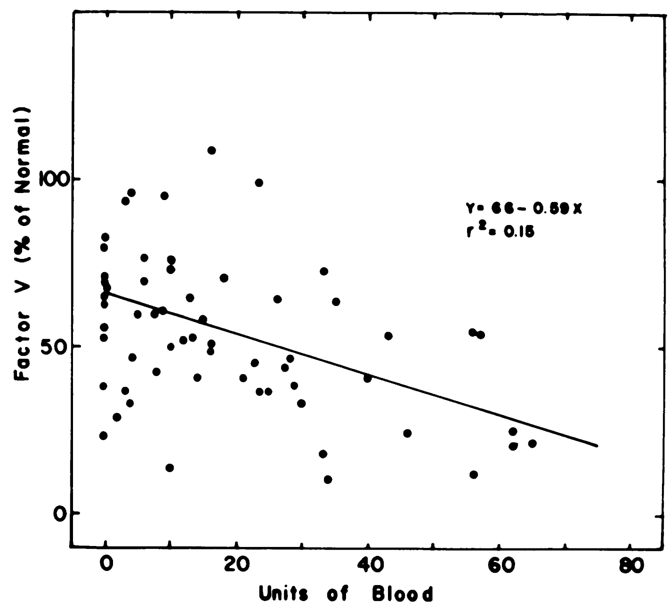

FIG. 3. Factor V levels in patients plotted against the number of units of blood transfused prior to the time the sample was obtained for assay. The regression was statistically significant: F = 14.92; 1.58 d.f.; p = 0.001.

wound. Data obtained when these patients had abnormal bleeding are presented in Table 3. In five patients, the coagulation factors were in the normal range. Three patients had consumption of platelets and fibrinogen as well as low levels of factors V and VIII, suggesting intravascular coagulation (DIC).

The mean number of units of blood received by the patients who bled, prior to the onset of medical bleeding was 35. There was no difference in the means of lowest platelet counts recorded for the patients who had abnormal bleeding and those who did not. Likewise, the differences between the means of the lowest levels of fibrinogen and factors V, VII, IX, and X for the two patient groups were not statistically significant. Factor VIII levels were significantly lower in the group of patients who had abnormal bleeding compared with those who did not. However, the lowest levels of factor VIII measured were greater than 30% of normal in all of the patients with medical bleeding except for two who had DIC (documented by low platelets and

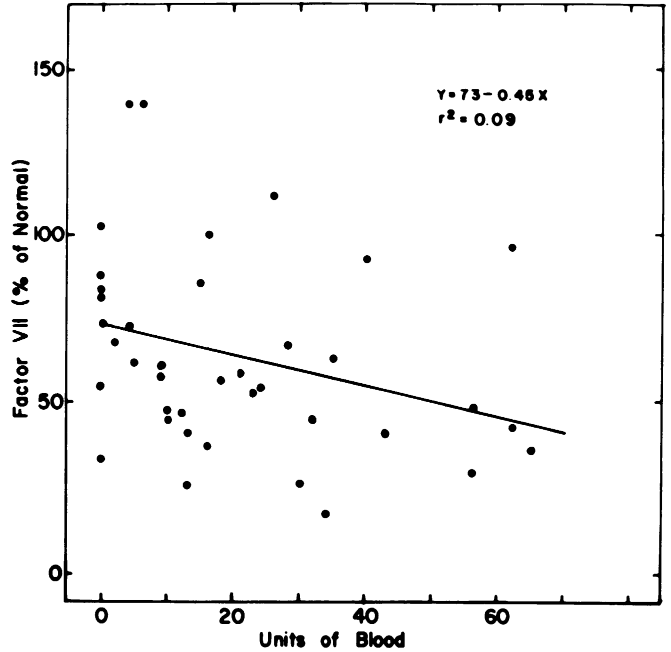

FIG. 5. Scatter diagram of factor VII plotted against units of blood transfused. The statistics for the regression are: F = 3.57; 1, 38 d.f.; p = 0.07.

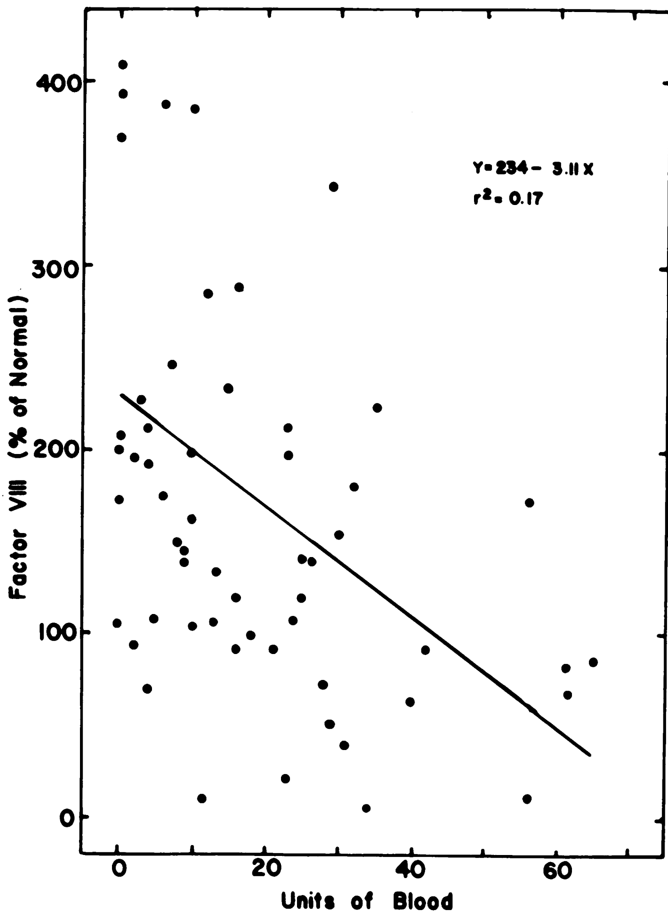

FIG. 4. Factor VIII levels in patients plotted against the number of units transfused prior to obtaining the sample. The regression was statistically significant: F = 11.68; 1,56 d.f., p = 0.001.

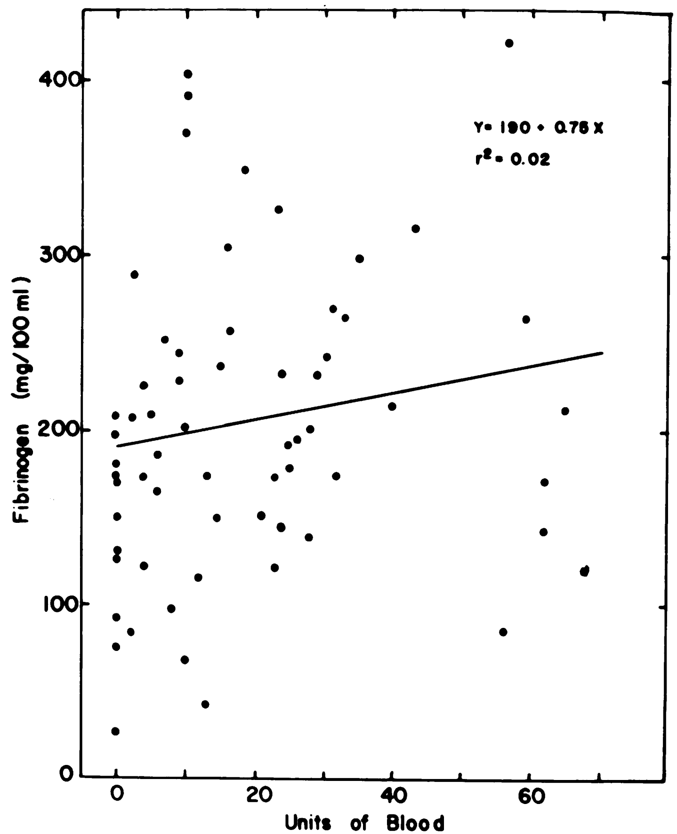

FIG. 6. Scatter diagram of fibrinogen plotted against units of blood transfused. The statistics of the regression are: F = 1.00; 1,60 d.f.; p = 0.32.

TABLE 3. *Hemostasis Tests and Treatment of Patients Having Generalized Bleeding*

Pt. No.	Clinical Problem	Levels at Time of Bleeding: Platelet Count	Fibrinogen	BT	VIII	V	Blood Components in First 48 hr of Admission: Mod. W.B.	Plate-lets	Cryopre-cipitate
10	Aortic aneurysm	140,000	198	20′	124	71	16	10	0
16	Aortic aneurysm	90,000	225	18′	192	96	35	14	0
18	Stab wound abdomen	60,000	117	30′	—	52	62	40	0
19	Soft tissue trauma. Retroperitoneal hematoma	50,000	173	23′	40	18	59	12	10
20	Severe chest trauma	70,000	307	21′	93	54	56	28	0
21	Post antrectomy for duodenal ulcer	32,000	28	30′	6	11	62	20	0
22	Aortic aneurysm	85,000	144	13′	108	37	30	12	6
23	Soft tissue trauma, skull fracture	81,000	68	17′	21	14	27	12	0

fibrinogen and evidence of ongoing consumption). There was good correlation between the levels of factors V and VIII and between factor VIII and fibrinogen in samples obtained from the patients who had medical bleeding, including the three who had abnormally low factor V and VIII levels.

Of the eight patients who had abnormal bleeding, six were treated only with modified whole blood and platelet concentrates. In each of these cases, bleeding was controlled shortly after platelet transfusions were given. The other two patients also received plasma or cryoprecipitate in addition to modified whole blood and platelets. In all patients, generalized bleeding was controlled within 12 hours of its onset. No patient in the study died as a direct consequence of bleeding or had uncontrolled bleeding at the time of death.

Screening Tests

The bleeding times, prothrombin times and partial thromboplastin times done at the time of bleeding in patients who had abnormal bleeding were compared with those performed on samples from patients without abnormal bleeding in order to assess the value of these screening tests for predicting whether a patient will develop abnormal bleeding. The ratio of the patient's clotting time to the normal plasma control clotting time was used to normalize the results.

Thirty-seven samples were obtained within 24 hours of admission from the 19 patients without abnormal bleeding. The mean of the prothrombin times in this group was 1.23 ± 0.14 (1 S.D.) times the control. The mean PTT was 1.12 ± 0.23 times control. For the eight patients who developed generalized bleeding, the mean PT at the time of bleeding was 1.63 ± 0.50 times the control and the mean PTT 1.68 ± 0.69 times the control. Although the means for the patients with generalized bleeding were considerably higher than those for non-bleeding patients, the variability was also greater. Indeed, the predictive value of the PT and PTT was poor when the results were analyzed according to whether patients with moderately abnormal PT and PTT had generalized bleeding or not (Table 4). For purposes of analysis, a level of 1.3 times the control was selected as moderate prolongation. This corresponds in our system to a PT of 19 seconds and a PTT of 53 seconds. Of samples in which the PT ≥ 1.3 times the control, seven were from patients with abnormal bleeding, eight were from patients without abnormal bleeding. Of nine samples with the PTT ≥ 1.3 times the control, five were from patients with abnormal bleeding, four were from patients without abnormal bleeding.

The PT and PTT were fair predictors of bleeding only when they were markedly prolonged. Of six samples where the PT and PTT were ≥1.5 times control (PT

TABLE 4. *Number of Patients Having Prolonged PT or PTT*

Patient Category	Prothrombin Time: <1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.	PTT: <1.3 × Control	>1.3 × Control	>1.5 × Control	Total No. Pts.
Generalized bleeding	1	7	4	8	3	5	4	8
No generalized bleeding	11	8	2	19	15	4	2	19
Total	12	15	6	27	18	9	6	27

For patients with bleeding, the results of tests at time of bleeding are tabulated; for non-bleeding patients, the longest PT and PTT.

22 seconds, PTT 62 seconds) four were from patients with abnormal bleeding, two from patients without abnormal bleeding.

In a similar way, the template bleeding times did not discriminate well between bleeding and nonbleeding patients because of large overlap. Although all patients with generalized bleeding had a BT $\geq$ 10 min and seven (88%) had a BT $\geq$ 15 minutes, 12 (63%) of patients without generalized bleeding had a BT $\geq$ 10 and nine (47%) had a BT $\geq$ 15 minutes at some time within the first two days of hospitalization. Thus, of 20 patients with a BT $\geq$ 15 minutes, 56% did not have generalized bleeding.

Discussion

By individualized component therapy and extensive component fractionation, it is possible for community blood banks to provide components needed by several patients from each unit of blood donated. Using a triple-bag system, for example, platelet concentrates, cryoprecipitated AHF and modified whole blood, lacking these fractions, can be produced. The applicability of this system depends upon the safety and efficacy of modified whole blood for transfusion in patients who have simultaneous volume and oxygen transport deficiencies requiring transfusions of whole blood.

We have sought to determine the composition of modified whole blood in regard to hemostatic components, to compare it with unfractionated whole blood, and to attempt to determine if an association exists between platelet and clotting factor levels in patients and the number of transfusions they received.

Platelets

There are several possible causes of thrombocytopenia in trauma patients. The most important are dilution by transfused blood or other fluids, and consumption of platelets. Platelets, in blood which is refrigerated, rapidly become nonviable.[11] Furthermore, adults, at least, have a limited ability to increase their platelet production acutely and have little or no readily mobilizable platelet pool.[16]

That transfusion of large volumes of blood should cause thrombocytopenia is therefore, relatively predictable. It has been suggested that as little as ten units of blood transfused into an adult may cause clinically significant thrombocytopenia. However, our results (Fig. 2) suggest that, on the average, the platelet count would fall below 100,000 after transfusion of 18 units of blood. Studies in normals have shown the bleeding time to be normal if the platelet count is 100,000/μl or greater unless there is platelet dysfunction.[6] This, it seems reasonable to anticipate that thrombocytopenia may become a clinically significant problem after an adult has received 15–20 units of blood (about 1.5–2.0 times his blood volume). Only two patients in our study had platelet counts less than 100,000 after having received less than 18 units of blood. One of these had a platelet count of 76,000 before any blood was transfused. This patient had a ruptured abdominal aortic aneurysm; it is probable that local consumption of platelets at the site of the aneurysm was responsible for the thrombocytopenia.

Slightly less than half the variation in platelet counts in this study could be ascribed to the functional relationship between blood transfused and the platelet count. A number of factors occurring in trauma patients cause platelet consumption. These include massive brain, lung or other soft tissue damage, severe shock, hypoxia, sepsis and endothelial damage.[14,17]

The most useful parameter for estimating the need for platelet transfusions in our patients was the platelet count. In contrast, the bleeding time proved to be of little help in predicting whether a trauma patient would have abnormal bleeding because the bleeding time was commonly prolonged in patients who did not develop microvascular bleeding as well as those who did. This agrees with the findings of Miller, et al.[10] who noted that the Ivy bleeding time was prolonged in all of their patients by the time they had received five units of blood and well before any patient developed abnormal bleeding. Thus, the bleeding time, in addition to being difficult to obtain under emergency operating room conditions, does not appear to be helpful in anticipating the onset of microvascular bleeding.

Coagulation Factors

The only clotting factors which are labile on storage at 4° are factors V and VIII. Fibrinogen and the vitamin K-dependent proenzymes are preserved in blood stored for 21 days at levels greater than 60% of their activities in fresh blood or fresh frozen plasma (Table 1). Thus, plasma transfusion is not needed to supplement modified or stored whole blood transfusions in patients with liver failure, vitamin K deficiency or warfarin anticoagulation who are bleeding.

Factor V is generally considered to be quite labile on storage at 4° in ACD blood.[21] Our data suggest that factor V, at least under present-day storage conditions, is not as labile as has been thought, the mean level remaining above 50% for more than two weeks. The clinical measurements also show that a patient's factor V level cannot be predicted from the number of units of modified whole blood he has received. Other variables which affect a patient's factor V level include

the rather large variation between normal individuals,[9] severe hepatic failure[5] and consumption.[17]

Factor VIII is the most unstable of the clotting proteins (Fig. 1), the level of CPD blood falling below 50% in less than 24 hours of storage at 4°. Like platelets, factor VIII cannot be effectively replaced by the transfusion of whole blood. However, our studies of factor VIII levels in trauma patients (Fig. 4) indicate that the level of factor VIII is rarely below 50%. Furthermore, although the slope calculated for the regression line in Figure 4 is, statistically, significantly different from zero, the low coefficient of determination (0.15) indicates that 85% of the total variability in the patients' factor VIII levels is attributable to causes other than dilution by the blood transfused.

Our data confirms other studies showing a large physiological reserve of factor VIII and higher than normal levels in patients after trauma or operations. As in the case of factor V, individual patients may have low levels, but the level cannot be predicated from the amount of blood transfused. Rather, the concordance between levels of factors VIII and V and fibrinogen suggests that consumption of these proteins is the major cause of the occasional deficiencies in our patients.

Other Clotting Factors

The results of assays of factor VIII and fibrinogen are representative of other clotting factor levels in the trauma patients. In each case, there was essentially no functional relationship between the amount of blood transfused and the measured activity of the protein.

This study demonstrates that transfusion of modified whole blood of random age to trauma patients needing large volumes of blood does not cause clinically significant clotting factor deficiencies. Thus, to supplement transfusions of modified whole blood with fresh blood or fresh frozen plasma, in order to provide clotting factors is unnecessary and wasteful. Platelet transfusions are frequently necessary after a patient receives blood transfusions in excess of about 1.5 times his normal blood volume.

These results have important implications for the management of blood resources. They suggest that the emphasis which many have placed on increasing the fraction of transfusions given as packed red cells is inappropriate. It has been recommended that up to 85% of transfusions should be given as red cells, and that albumin or frozen plasma be given if additional volume is needed. In our region, 37% of the blood transfused is given to patients who receive five or more units of blood, patients who require volume expansion as well as oxygen transport capacity. An unrealistically high use of red blood cells tends to increase the demand for albumin and plasma.

Eight of the 27 patients in our study developed generalized oozing, usually at the time of operation. In six of these (Table 3), the bleeding was controlled with platelet transfusions. In five of the six, the platelet count at the time of bleeding was $<100,000/\mu l$ and clotting factors were adequate for hemostasis. The sixth had a platelet count of 140,000 but bleeding was rapidly controlled after administration of six units of platelets.

The most useful readily available laboratory tests for predicting abnormal bleeding and guiding therapy proved to be the platelet count and fibrinogen level. The PT, PTT, and BT correlated well with generalized bleeding when they were markedly prolonged, but many patients who did not develop generalized bleeding had moderate abnormalities of these tests.

We recommend that patients who need both red cells and volume replacement be treated with whole blood or modified whole blood rather than with red cells and albumin or plasma. When a patient receives more than 15 units of blood, the platelet count should be followed and the surgeon should be alert to signs of generalized oozing. Platelet concentrates are usually indicated if a patient receives over 20 units of blood in a 12 hour period. If abnormal bleeding occurs, platelet concentrates should be given and the platelet count coagulation tests obtained in order to make a specific diagnosis, the most likely disorders to be considered being dilutional thrombocytopenia and DIC. Valuable time for selection of proper therapy may be lost by the presumption that clotting factors have been diluted by transfused blood.

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Erratum

In the article "Critical Evaluation of Hypertonic and Hypotonic Solutions to Resuscitate Severely Burned Children: A Prospective Study" by Fred T. Caldwell, M.D. and Bonny H. Bowser, B.S. (Ann. Surg., 189:546, 1979) the formula appeared incorrectly.

The formula *should* read: ml/kg·% and *not* ml/kg/dl.