Fresh Frozen Plasma Supplement to Massive Red Blood Cell Transfusion

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The efficacy of supplemental fresh frozen plasma (FFP) therapy after massive packed red cell (PRBC) replacement for hemorrhagic shock was studied in 22 conditioned dogs. Ten dogs were randomized to received FFP, balanced electrolyte solution (BES), and PRBC, while 12 dogs received BES and PRBC. Coagulation factor activity for Factors I, II, V, VII and VIII, as well as antithrombin III (AT III), prothrombin time, partial thromboplastin time, and thrombin time, were measured at preshock, postshock, postresuscitation, and postshock day two. All coagulation factor activities fell with shock and decreased further with resuscitation in both groups. Factor II (a procoagulant) and AT III (an anticoagulant) fell significantly less after resuscitation in the plasma dogs; otherwise, no postresuscitation differences were seen. The changes in factor activity from postresuscitation until day two reflected factor half life and molecular weight, independent of FFP therapy. These data show that prophylactic FFP therapy does not efficiently restore coagulation activity. Consequently, routine FFP therapy for its procoagulant effects after hemorrhagic shock should be abandoned pending controlled studies in man.

THE RESUSCITATION REGIMEN for hemorrhagic shock has evolved over many years.[1-3] Because of postshock homeostatic fluid shifts into both the interstitial fluid and the intracellular fluid spaces, whole blood replacement alone failed to meet total body needs. Consequently, whole blood infusion was supplemented with balanced electrolyte solution (BES) to accommodate obligatory expansion into the extravascular fluid spaces. Postresuscitation reductions in total serum proteins, especially serum albumin, led to supplementation with commercially prepared human serum albumin solutions. Specific reductions in coagulation proteins were treated by fresh frozen plasma (FFP) infusions. Usually, the FFP therapy was empiric with 1 unit FFP being given for every five or six transfusions of whole blood.[4,5] Deficiencies in the coagulation cascade (secondary hemostasis) were rarely documented.[6,7]

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During the past 10 years two events have modified, further, the resuscitation regimen for hemorrhagic shock. First, multiple controlled studies on the therapeutic benefits of human serum albumin supplementation showed either no benefit or else injurious effects on visceral function and on coagulation function.[8,9] Second, the blood banking industry placed greater emphasis on specific component therapy, thus making whole blood relatively unavailable for rapid replacement in patients with severe hemorrhagic shock.[6,7] Consequently, concern for profound postresuscitation hypoproteinemia, reduced serum oncotic pressure, and lowered coagulation protein content lead to a ten-fold increase in FFP usage in 10 years. Although this dramatic increase in FFP usage is designed to restore coagulation proteins, no controlled studies in man or animals address this issue. The present study was designed to determine, in a controlled canine hemorrhagic shock model, the effects of supplemental FFP on postresuscitation coagulation activity and secondary hemostasis.

Materials and Methods

The efficacy of supplemental FFP therapy in the resuscitation regimen for hemorrhagic shock was studied in 24 conditioned male dogs with an average weight of 22 kg (range: 18–26 kg). Phlebotomy of 500 ml blood was obtained through an external jugular vein at both 6 and 3 weeks before the shock insult. The blood was collected in citrate-phosphate-dextrose-adenine ($CPDA_1$) blood bags. Each unit was separated within 4 hours into packed red cells (PRBC) and FFP according to standard procedures of the American Association of Blood Banking. The PRBC was stored at 4 C, and the FFP was stored at −70 C to preserve the labile coagulation Factors V and VIII. Additional blood specimens were obtained from each dog at 6 weeks to establish a "normal pool" of canine plasma and serum proteins, prothrombin time (PT), partial

thromboplastin time (PTT), and thrombin clotting time (TT). After phlebotomy, one liter of BES was infused into each animal. All animals were maintained on a high protein diet. After the second phlebotomy at 3 weeks prior to hemorrhagic shock, intravenous fluids were administered, the animal was anesthesized (induction with Biotal® and maintenance with methoxyflurane), and splenectomy was performed through an upper abdominal midline incision. Before removing the spleen, autotransfusion was performed by first ligating the arterial inflow and then manually compressing the spleen until it had a contracted appearance. Two liters BES were given during splenectomy.

Three weeks after splenectomy, hemorrhagic shock was induced using a reservoir technique. The animals were anesthesized (Biotal, atropine, and methoxyflurane), intubated, and maintained on a pressure cycled ventilator. Left femoral artery and venous catheters were placed and a Swan-Ganz pulmonary artery catheter was passed through the right jugular vein. Pulmonary and systemic arterial pressures were measured using Statham pressure transducers (Statham Medical Instruments Inc., Oxnard, CA) and Gilson 4-channel chart recorder (Gilson Medical Electronic, Inc., Middleton, WI). The animal was administered heparin (100 units/kg) systemically, and the experiment continued only if the animal had an initial mean arterial pressure (MAP) above 100 torr. Using light anesthesia, the dogs were bled by way of the femoral artery catheter down to an MAP of 60 torr for 90 minutes, then to 40 torr for 30 minutes. MAP was regulated by withdrawing or returning blood from the reservoir as needed. Following this hemorrhagic shock insult, resuscitation was initiated and the dogs, by random selection, received either FFP (plasma group) or no FFP (Ringers group).

The sequence of resuscitation was designed to mimic the clinic setting. Initially, the dogs were resuscitated with a volume of 20 ml/kg body weight; the 20 ml consisted of lactated Ringers solution in the Ringers group and consisted of 9 ml Ringers solution plus 11 ml autologous banked FFP in the plasma group. Next the dogs received autologous PRBC diluted in normal saline to a hematocrit of 40%; the volume of this diluted PRBC was equal to the reservoir volume in each animal. The final volume expansion was completed with the infusion of 30 ml/kg per kilogram of body weight. This 30 ml consisted of lactated Ringers solution in the Ringers group and 19 ml lactated Ringers solution plus 11 ml FFP in the plasma group. Both groups received the same total volume replacement during resuscitation, which averaged 922 ml PRBC solution and 1100 ml BES or BES plus FFP. After the shock insult was terminated, the reservoir blood was drained into $CPDA_1$ blood bags and separated into PRBC and FFP using the above techniques. The PRBC was discarded and the FFP was stored at −70 C for reinfusion on postshock day 2. After resuscitation, the dogs were returned to their cages where they received oral water as tolerated. On postshock day 1, the dogs received 50 ml/kg body weight; this infusion consisted of 50 ml of Ringers lactate for the Ringers group and the combination of 38 ml lactated Ringers solution plus 12 ml FFP for the plasma group.

On postshock day 2, final blood samples were drawn and the animals were reanesthetized. A femoral artery catheter and a Swan-Ganz pulmonary artery catheter were inserted. An incision was made in a hind limb over the proximal saphenous vein and a large lymph vessel was isolated and cannulated. Lymph bundles adjacent to this area were ligated proximally. A 22-gauge catheter was then advanced into this lymph channel, taking care to keep the catheter tip away from lymph valves to assure the free flow of lymph once the catheter was secured with ligature. The hind limb was then passively exercised at a rate of 20 movements per minute to facilitate lymph flow and collection.

Measurements made during this study included the clotting times (PT, PTT, TT), coagulation protein factor activity (FI, FII, FV, FVII, FVIII), AT III activity, hemoglobin, electrolytes and hematocrit.[11] These measurements were made on serum collected at 6 weeks before shock (normal pool), the banked FFP, reservoir FFP, and in the serum samples collected before shock, at the end of shock, 30 minutes following the completion of resuscitation, and on day 2. These studies were also measured in the lymph samples collected on day 2. All samples collected after heparin was administered were neutralized with protamine sulfate before measurement. Statistical analysis was performed by MANOVA to show that the two groups were comparable before shock and at the end of shock; differences between the two groups after resuscitation by the two treatment modalities were analyzed by Bonferroni's adjustment. Differences between the total group of 22 dogs when compared to a previous analysis were made by a Student's t-test.

Results

The preshock or basal state clotting times (PT, PTT, TT), the coagulation factor activities for FI, FII, FV, FVII, and FVIII, as well as the AT III activity, were similar to the pooled plasma samples obtained from the dogs at 6 and 3 weeks before shock (Table 1). The preshock hematocrit averaged 45% and was similar to the prephlebotomy samples, which averaged 46%. Thus, the dogs were fully recovered from the two phlebotomies and the splenectomy. Coagulation factor activity, AT III activity, and clotting times in the banked FFP that was used for resuscitation in the plasma group were also similar to the preshock basal levels (Table 1). Coagulation factor activity in the reservoir FFP tended to be lower than that in the

TABLE 1. *Coagulation Factors, Antithrombin III, Clotting Times in Basal, Banked, and Reservoir Fresh Frozen Plasma*

Times (Mean ± SE)		I (mg %)	II (%)	V (%)	VII (%)	VIII (%)	AT III (%)	PT (sec)	PTT (sec)	TT (sec)
Preshock	BES	178 ± 19	104 ± 5	105 ± 6	138 ± 15	170 ± 55	111 ± 4	6.8 ± 0.2	10.7 ± 0.1	10.9 ± 0.4
	FFP	189 ± 17	110 ± 3	110 ± 6	133 ± 10	100 ± 10	114 ± 2	6.7 ± 0.1	10.9 ± 0.3	10.4 ± 0.5
Banked FFP	BES	117 ± 23	99 ± 4	101 ± 7	138 ± 17	92 ± 13	100 ± 3	9.2 ± 1.6	12.3 ± 1.0	13.3 ± 1.4
	FFP	114 ± 19	94 ± 6	92 ± 7	102 ± 14	75 ± 7	102 ± 2*	7.8 ± 0.4	12.0 ± 0.6	11.5 ± 0.4
Reservoir FFP	BES	128 ± 15	66 ± 3	76 ± 6	75 ± 10	1.6 ± 0.4	86 ± 4*	12.6 ± 0.5*	—	—
	FFP	142 ± 16	69 ± 3	73 ± 6	77 ± 8	5 ± 4*	85 ± 2*	12.4 ± 0.5	—	—

* $p < 0.0055$ by MANOVA and Bonferroni's adjustment.

preshock serums; this tendency was statistically significant for FVIII. Consequently, the amount of FVIII infused in the plasma group of dogs on postshock day 1 was insignificant.

The shock insult was tolerated by 22 of the 24 dogs, and these dogs were successfully resuscitated. During resuscitation, the MAP in these 22 dogs was restored to at least 100 torr. The other two dogs died at the end of the shock insult before randomization into one of the two treatment groups. These two animals were excluded from all analyses. The volume of shed blood averaged 922 ml for the two groups, and both groups had a similar reservoir volume. The hemorrhagic shock insult caused a significant fall in all coagulation factor activity and in AT III activity resulting in a rise in all clotting times (Table 3). The per cent decrease in coagulation factor activity ranged from 20 to 40% when compared to the preshock coagulation factor activity. However, the percent coagulation protein activity after shock was still within the range for adequate maintenance of the coagulation cascade and the formation of a fibrin plug (secondary hemostasis).

Serum factors measured 30 minutes after the completion of resuscitation showed a further decrease in coagulation factor activity and AT III activity (Table 2). When the postresuscitation studies in all 22 dogs were compared with the postshock (preresuscitation) values, this fall in coagulation factor activity was statistically significant for FII, FV, FVII, and FVIII. When the postresuscitation values in the plasma group were compared to the Ringers group, the postresuscitation reduction in FII and AT III activity was significantly less in the plasma group (Table 3). Neither the plasma group nor the Ringers group had significant changes in the PT or PTT in response to resuscitation (Table 3). The TT, however, decreased toward normal in both groups in response to resuscitation; this change toward normal was similar for both groups (Table 3). All dogs in both groups appeared healthy on the day after resuscitation and thrived until the day 2 studies.

All clotting times (PT, PTT, TT) in both groups were normal and similar on the postshock day 2 studies (Table 3). The coagulation protein factor activity on day 2 either rose or fell in a similar manner in both groups with no particular relationship to FFP therapy or Ringers therapy. Thus, FI rose significantly from 88 mg% to 343 mg% in the Ringers group and from 104 mg% to 339 mg% in the plasma group; FII and AT III levels stayed nearly the same in both groups; FV rose minimally in both groups; FVIII increased moderately from 51% to 80% ml% in the Ringers group and from 50% to 86% in the plasma group; FVII fell from 57% to 44% in the Ringers group and from 68% to 44% in the plasma group (Table 3). The changes in coagulation protein factor activity and AT III activity from postresuscitation until day 2 were similar for both groups.

These paradoxical changes in coagulation protein factor activity and AT III activity from the postresuscitation period until the day 2 studies raised questions regarding the mechanisms by which serum coagulation factor concentration or activity is controlled. This question was ad-

TABLE 2. *The Effects of Shock and Resuscitation on Coagulation Factors, Antithrombin III, and Clotting Times*

Times (Mean ± SD)	FI (mg %)	FII (%)	FV (%)	FVII (%)	FVIII (%)	AT III (%)	PT (sec)	PTT (sec)	TT (sec)
Prephlebotomy Pool	203	140	94	107	89	—	6.3	11.0	10.9
Preshock (N = 22)	183.6 ± 12.3	106.6 ± 2.7	107.5 ± 4.3	135.9 ± 8.7	133.2 ± 27.2	112.1 ± 2.1	6.8 ± 0.1	10.8 ± 0.2	10.7 ± 0.3
Postshock (N = 22)	132.7* ± 10.1	81.2 ± 2.3	77.1* ± 4.1	94.9* ± 6.1	99.2* ± 9.8	86.1* ± 1.9	7.9* ± 0.4	15.1* ± 1.0	14.6* ± 1.1
Postresuscitation (N = 22)	96.0† ± 7.3	66.5† ± 2.3	39.3† ± 3.3	62.2† ± 5.2	50.0† ± 3.0	80.2† ± 2.0	8.4 ± 0.2	13.5 ± 0.3	10.8† ± 0.3

* 0.05 by Student's t test preshock *vs.* postshock.

† 0.05 by Student's t test postshock *vs.* postresuscitation.

TABLE 3. *Effect of Plasma Resuscitation on Coagulation Factor Activity, Antithrombin III, Clotting Times*

Postresuscitation (Mean ± SD)	I (mg %)	II (%)	V (%)	VII (%)	VIII (%)	AT III (%)	PT (sec)	PTT (sec)	TT (sec)
BES	88.1 ± 8.5	59.0 ± 1.8	36.3 ± 5.4	56.6 ± 6.4	50.7 ± 4.9	73.1 ± 2.5	8.5 ± 0.3	12.9 ± 0.3	10.7 ± 0.6
FFP	103.9 ± 11.8	74.1* ± 2.9	42.4 ± 4.0	67.7 ± 8.1	49.4 ± 3.8	86.7* ± 1.4	8.2 ± 0.2	14.2 ± 0.6	10.9 ± 0.4

* $p < 0.0055$ by MANOVA and Bonferroni's adjustment.

dressed by comparing the combined effects of coagulation protein factor molecular weight and half-life on the changes from postresuscitation until day 2. Each of these factors was given equal weight on a scale from 0–100 units and then compared with the per cent change from postresuscitation until day 2 (Table 4). This weighted scale demonstrates that day 2 coagulation factor activity appears to be a function of molecular weight and factor half-life. Factor VII, which has a short half-life and a relatively small size decreases from postresuscitation until day 2, whereas, FI which is relatively large and has a long half-life increases markedly from postresuscitation until day 2 (Figs. 1 and 2).

Measurements of lymph on postshock day 2 demonstrated no measurable activity of FI, FV, or FVIII in either group. FII measurements averaged 5% in each group whereas FVII averaged 2% in each group. All of the clotting times were grossly prolonged. These extremely small levels of coagulation factors in the lymph were surprising since the lymph tended to clot unless appropriate precautions were made. Further studies on coagulation factor activity in lymph needs to be performed.

Discussion

The formation of a fibrin clot (secondary hemostasis) results from multiple complex reactions, many of which are not fully understood.[12,13] The initial stimuli for setting into motion the coagulation cascade leading to secondary hemostasis actually occur during the early stages of primary hemostasis (formation of a platelet clot). Once initiated, secondary hemostasis evolves through two systems, namely, the intrinsic and the extrinsic pathways. Both pathways lead to a common pathway or the formation of activated Factor X (FX_A), which combines with Factor V and calcium to form thrombin from prothrombin.

TABLE 4. *The Coagulation Factor Molecular Weights (MW) and Half Lives*

	MW (kD)	$t_{\frac{1}{2}}$ (Hours)
Factor I	340	96
Factor II	69	87
Factor V	400	24
Factor VII	45	5
Factor VIII	2000	12

Thrombin, in turn, cleaves fibrinogen resulting in fibrin. The intrinsic pathway involves the sequential activation of Factors XII, XI, IX, and VIII and may be monitored by the PTT. The extrinsic pathway utilizes activated Factor VII and may be monitored by the PT.

Hemorrhagic shock, by itself, causes significant changes in coagulation factor proteins.[12] This was reflected by the significant fall in all five coagulation factor protein activities and in the AT III activity by the end of the shock insult. This decrease in the procoagulant factor protein and heparin cofactor (AT III) levels likely results from dilution of the plasma volume from the influx of fluid out of the interstitial fluid space during acute hemorrhage. Since the coagulation factor proteins have a lower concentration within the interstitial fluid space, the effect of such a vascular influx from the interstitial fluid space would be dilution of all proteins. Alternatively, the coagulation factor proteins may have been consumed; this seems unlikely, however, since the site of bleeding was confined to a femoral artery canula and not to multiple visceral perforations or uncontrolled hemorrhage from a peptic ulcer, as might be seen in the clinical setting.[4,13] Also, shock insult may directly affect coagulation proteins; thus, the reduction in some of the coagulation factor proteins in the reservoir plasma that was used for reinfusion on day 1 might be due to such an insult. Regardless of

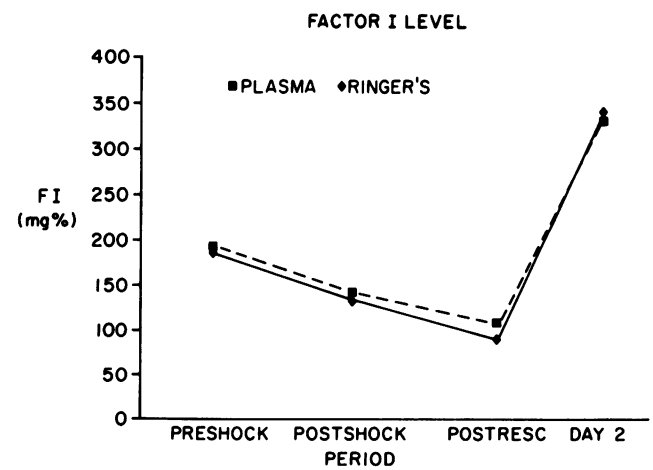

FIG. 1. All factor activities fell after the shock insult and decreased further by the end of resuscitation in both groups. Factor I activity rose to supernormal levels by day 2 and was the same for both groups.

mechanism, this postshock reduction in coagulation factor proteins has stimulated the routine addition of FFP to standard resuscitation regimens for treatment of hemorrhagic shock. This use of FFP is designed to restore coagulation factor protein activity.

Interestingly, resuscitation from shock produced a further acute decline in coagulation factor proteins, both in animals receiving Ringer's lactate and those receiving FFP. Once could ascribe this reduction in coagulation factor proteins to dilution after Ringer's lactate resuscitation. Such an explanation is less tenable in the plasma animals that received PRBC diluted in saline plus the large volume of FFP. Current recommendations for FFP supplement to the resuscitation regimen for hemorrhagic shock consist of the addition of about 1 unit of plasma for every six transfusions of PRBC. The infusion of 750 ml or 3 units FFP over 24 hours in the plasma group represents approximately 50% of the dogs' average blood volume. This would be equivalent to the infusion of approximately 2500 ml FFP or 10 units in the average-sized patient. Currently, this is more than sufficient to meet current popular clinical recommendations for FFP supplement for restoring coagulation factor proteins after hemorrhagic shock. Furthermore, the fall in coagulation factor proteins after resuscitation with plasma did not result from deficient factor activity in the infused FFP. Indeed, the banked FFP had normal levels of coagulation factor proteins, thus reflecting the careful handling, rapid separation, and early freezing following the current guidelines of the American blood banking industry. The only significant change between the two groups after resuscitation was that the coagulation factor activity of FII (prothrombin) and AT III (heparin cofactor) fell significantly less in the plasma group than in the Ringer's group. Even these two changes may have offsetting effects, since FII functions as a procoagulant whereas AT III functions an anticoagulant.

The convalescent or day 2 findings document clearly the multifactorial influences on the coagulation factor protein activity. Regardless of whether the animals received Ringer's lactate or plasma during resuscitation and on postshock day 1, the day 2 studies of the coagulation factor activity and AT III activity were almost identical for both groups and correlated directly with both the molecular weight and factor half-life (Fig. 3). Presumably, the factor half-life has an important influence on convalescent coagulation factor protein level when the liver is still recuperating from the shock insult and not yet synthesizing coagulation proteins in a normal manner. The coagulation protein molecular weight likely influences the day 2 concentrations by regulating the ratio of the intravascular/extravascular coagulation protein level and, therefore, activity. Unfortunately, this conclusion regarding extravascular protein flux was not supported by the day 2 lymph concentration of coagulation proteins, which

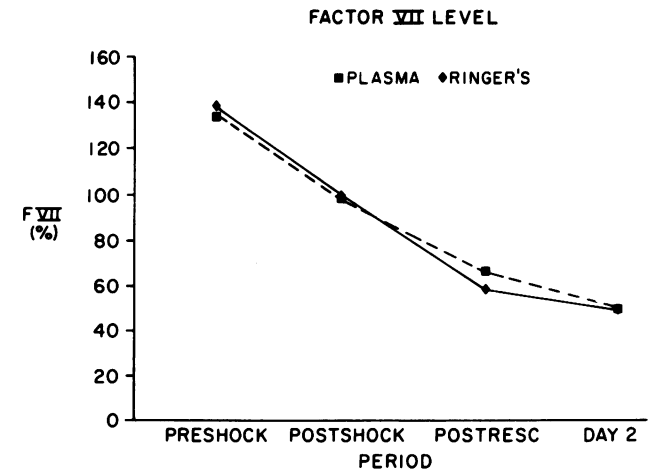

FIG. 2. Factor VII activity also fell after the shock insult and again by the end of resuscitation. This occurred equally in both groups. In contrast to Factor I activity, the day 2 level of Factor VII activity was lower than the postresuscitation level. This change was identical in both groups.

were very low in both groups; clearly, more work in this area is needed. Since both groups responded similarly by day 2, coagulation factor synthesis, degradation and consumption likely had no bearing on day 2 levels. Since prior studies in man and animals demonstrated that resuscitation with supplemental albumin leads to a reduction in all serum nonalbumin proteins, including the coagulation factor proteins, a reassessment of these findings needs to be conducted to determine whether the reduction in coagulant factor proteins after albumin resuscitation occurs in both the acute and the convalescent phases.[8,10,14]

Based upon these controlled canine studies, the role of routine FFP supplementation of the resuscitation regimen for hemorrhagic shock must be challenged. The shock insult used herein was severe, reflecting an acute reduction

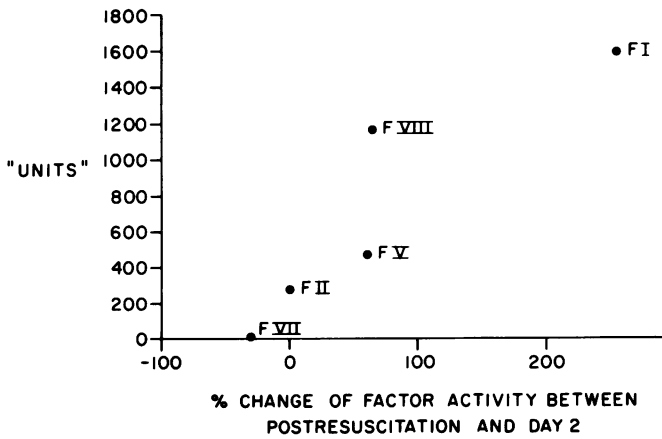

FIG. 3. "UNITS" derived equally from factor molecular weight and half-life relate directly to the per cent change in factor activity from postresuscitation until day 2.

in two-thirds of the normal blood volume. Although the hemorrhage was severe and carefully controlled, one cannot translate the results of an animal study to the clinical arena. Based upon these findings, however, controlled studies in man are needed to define the proper role of FFP therapy for restoration of coagulation proteins after clinical hemorrhagic shock.

This study does not fully address the question of FFP supplement for potential colloid or immune affects.[15] Further studies on hemodynamic and immune responses and sequential protein changes in serum and lymph after either plasma or Ringer's resuscitation are needed. Despite these limitations, these data demonstrate that supplemental FFP in this setting does not enhance the coagulation picture. During extensive plasma exchange without hypovolemic shock, removal of the total circulating plasma volume does not reduce the coagulation protein activity below an effective level.[16] Maintenance of coagulation proteins after exchange results from interstitial fluid space relocation of these factors. A similar restoration likely occurs after a severe hemorrhagic insult of one circulating blood volume; the main difference would be delayed liver synthesis of all proteins due to the shock insult.[16] Pending controlled studies in man, the routine use of plasma supplementation in the resuscitation regimen for hemorrhagic shock should be abandoned. Moreover, the use of FFP should be restricted to those individuals who have a bleeding insult that surpasses circulating one volume or to those patients with continued oozing due to a defined defect in the coagulation cascade.[16] Finally, more clinical studies are needed to better define the total role, if any, of FFP therapy in hemorrhagic shock. The lack of a defined benefit in such studies may curtail the precipitous use of FFP and abolish the exorbitant cost of unwarranted FFP therapy.[15]

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Discussion

DR. ROBERT J. BAKER (Chicago, Illinois): Dr. Martin has presented an extremely important paper because fresh frozen plasma has become the second most commonly used blood component, exceeded only by packed red cells, in surgical practice in the last decade. In actuality, the only clotting factor that is provided by fresh frozen plasma exclusively is factor 5, or labile factor. Factor 5 is also present in bank blood less than 7 days old, although packed red cells, because they have only half as much plasma as whole blood, have half as much factor 5, and that is the usual initial blood component administered.

Factor 8 and fibrinogen are more efficiently provided as cryoprecipitate, and there is a current trend to a much wider use of cryoprecipitate than was true a number of years ago. This is largely due to the experience in cardiovascular surgery; there is now a lesser use of fresh frozen plasma in major hemorrhage, massive trauma, and other extensive operations.

There are really two cogent reasons to support the contention of the authors that there is too much fresh frozen plasma being infused, the first of which is the cost, between $35 and $50 a unit, and secondly, the serum hepatitis risk, which is essentially the same with fresh frozen plasma as it is with whole blood, approximately 0.2% per unit. If 5 units of fresh frozen plasma are given, the hepatitis attack rate, at least theoretically, would be 1%, 10 units 2%, and so on.

It is hard to disagree with the conclusions of this paper, but several questions need to be addressed if there is advocacy of stricter criteria for use of dangerous and very expensive treatment modalities.

First, I would like to ask the authors how applicable the conclusions drawn from this carefully controlled, canine modified Wiggers shock preparation are to the patient in shock from major hemorrhage and/or trauma. For example, shock patients often become significantly hypothermic either before or during operation, which affects both platelet function and the ability of the liver to generate procoagulants. Was the temperature modified in these animals to simulate more closely the clinical setting?

In addition, I would like to ask what happened to platelet numbers in these animals? We are seeing more thrombocytopenia now that we look for it, as a manifestation of subclinical or even overt disseminated intravascular coagulation. Usually this is evident first as a fall in platelets, so the question is did platelet function and numbers diminish in these experimental animals?

The vastly more complex clinical abnormalities resulting from shock, including hypoxic hepatic dysfunction, need to be entered into this equation as well to justify the basic change in treatment philosophy suggested by this model. I suppose that we could say that blood component therapy is akin to contraception; the safest and least expensive course is total abstention, but that is not ordinarily the course that is chosen.