Prophylactic Fresh Frozen Plasma Administration: Failure to Reduce Blood Loss or Transfusion Requirements after Routine Cardiopulmonary Bypass

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Abstract

Cardiopulmonary bypass may result in a variety of coagulation disorders, some of which result in overt hemorrhage. The routine use of blood products to normalize clotting factors in the post-bypass period is expensive and may subject the patient to the risk of hepatitis and isoimmunization. We studied the effects of routine administration of four units of fresh frozen plasma (FFP) on standard clotting factors, mediastinal blood loss, and transfusion requirements in a randomized prospective fashion. Twenty-seven patients received plasma and 26 did not. There were no differences in the preoperative clotting studies, blood counts, liver functions, pump time, cross clamp time or type of surgery between the groups.

No differences were noted between the two groups in homologous blood requirements, clotting parameters or mediastinal blood loss. Patients receiving FFP had slightly lower hematocrits in the early postoperative period.

The routine use of FFP had no discernible effect on post-bypass hemorrhage or blood usage in a series of open heart operations, most of which were coronary revascularization. The clotting factors in the single reoperated patient were normal. Technical factors and precise heparin reversal play a more important role in postoperative hemostasis than plasma. We cannot recommend the routine administration of FFP after cardiopulmonary bypass.

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Introduction

For many years surgeons have been seeking ways to minimize postoperative hemorrhage in patients undergoing cardiopulmonary bypass. Systemic anticoagulation and its reversal, mechanical trauma to blood elements, sequestration of platelets and alteration in the delicate clotting and fibrinolytic systems all have contributed to the occasional bleeding diathesis seen in the early postoperative period.[1,2,3,4,5]

Fresh frozen plasma (FFP) contains many clinically significant labile clotting factors and has in the past[6] been administered prophylactically to forestall subtle coagulopathies that have been attributed to changes in the levels of procoagulants due to surgery and bypass techniques. Because FFP carries added expense, an additional drain on blood bank resources,[6] and a danger of transmitting hepatitis, a study was designed to assess the effect of routine post-bypass administration of FFP on postoperative bleeding, blood requirements and routinely measured plasma clotting factors.

Methods

Fifty-three consecutive patients were studied in a randomized prospective manner, using hospital

numbers. The only exclusion was a 20-year-old male with sudden catastrophic aortic insufficiency secondary to infectious endocarditis who was moribund on admission, and for whom clotting studies were unavailable. Twenty-six patients (Group I) received a mean of 3.73 units of FFP immediately after bypass as Protamine was being administered. Twenty-seven patients received no plasma (Group II). A disposable bubble oxygenator with a clear balanced electrolyte prime was employed and bypass was carried out at 24 to 28 degrees centigrade. Cold potassium cardioplegia effected ischemic arrest in all cases. Systemic heparinization was accomplished with 3 mg. per kg. as the initial dose. The activated clotting time (ACT) was monitored throughout the bypass period and never allowed to fall below 480 seconds. Protamine dosage was back-calculated by the use of standard dose response curve protocols.[7] If filling pressures were high, FFP was administered slowly in lieu of residual oxygenator blood and this pump blood was subsequently washed, centrifuged and administered later in the recovery period. Administration of the FFP was generally complete by the time the patient left the operating room.

Determinations of hemoglobin and hematocrit values, prothrombin time, partial thromboplastin time, platelet counts and fibrinogen levels were made in the recovery room and on the morning of the first and second postoperative days. Mediastinal drainage was measured at 24 and 48 hours after the patients arrived in the intensive care unit. When there was no drainage (QNS) for eight hours, the tubes were removed; therefore, some patients had no additional drainage reported after 24 hours.

Blood transfusions for whole blood and packed cells were recorded as units and no patient received any blood after leaving the ICU. Blood transfusions were used to correct hypovolemia as determined by measurements of cardiac output and pulmonary capillary wedge pressure in conjunction with measurements of urine output and mediastinal blood loss.

Patient Data

Patients in Groups I and II were similar in the ratio of males to females, preoperative clotting parameters, bypass and aortic cross clamp times and operations performed (Table I). Twenty patients in Group I had coronary artery bypass grafting (CABG), one patient had a mitral valve replacement plus CABG, one had an aortic valve replacement, one had a mitral valve replacement, one had an atrial septal defect repaired, and one had CABG plus septal myomectomy. In Group II there were 23 patients who had CABG, one CABG plus aortic valve replacement, and one mitral valve replacement. There were no perioperative deaths in either group.

Statistical analysis utilized the Yates corrected Chi-square analysis and analysis of variance for repeated measures. Significance was assumed at the $p = 0.05$ level.

Results

Clotting parameters are shown in Table II. There were no significant differences in any of the

TABLE I
Comparison of Patients

	Group I	Group II	Significance
Male/Female	19/7	24/3	NS
Hemoglobin	13.68 + 1.87	14.34 ± 1.57	NS
Hematocrit	40.75 ± 5.20	42.70 ± 4.70	NS
Fibrinogen	351 ± 99	319 ± 75	NS
Platelets	236M ± 69M	225M ± 56M	NS
Pump Time	111 ± 29 min.	107 ± 27 min.	NS
Cross Clamp Time	56 ± 21 min.	55 ± 17 min.	NS
Operation	20 CABG+ 2.35 grafts/pt	22 CABG+ 2.72 grafts/pt	NS

* CABG = Coronary artery bypass graft
NS = Not significant ($p > 0.05$)

TABLE II
Post Operative Hematologic Parameters

	Group I	Group II	Significance
	Recovery Room	Recovery Room	
Hematocrit	30.52 ± 4.72	35.15 ± 5.6	$p < 0.01$
Hemoglobin	10.19 ± 1.75	11.82 ± 1.75	$p < 0.003$
Fibrinogen	258 ± 87	245 ± 64	NS
Platelets	116M ± 51M	162M ± 66M	NS
PT/PTT	12.2 ± 3.31/N	13.60 ± 4.08/N	NS
	POD #1	POD #1	
Hematocrit	35.92 ± 4.20	39.15 ± 5.75	$p < 0.01$
Hemoglobin	13.18 ± 1.49	13.36 ± 1.99	$p < 0.003$
Fibrinogen	309 ± 73	290 ± 64	NS
Platelets	145M ± 48M	144 ± 43	NS
PT/PTT	12.20 ± 3.32/N	12.60 ± 3.74/N	NS
	POD #2	POD #2	
Hematocrit	35.23 ± 5.73	37.30 ± 6.25	$p < 0.01$
Hemoglobin	11.68 ± 1.75	12.9 ± 2.00	$p < 0.003$
Fibrinogen	418 ± 123	446 ± 162	NS
Platelets	128M ± 49M	110M ± 48	NS
PT/PTT	11.00 ± 1.7/N	11.40 ± 2.0/N	NS

PT/PTT = Prothrombin time/partial thromboplastin time
NS = Not significant ($p > 0.05$)
POD = Post-operative day

postoperative hematologic variables obtained in the recovery room or on postoperative days one or two except for a lower hematocrit and hemoglobin value for Group I. This was attributed to the hemodiluting effect of the red cell-free plasma in the immediate postoperative period.

There was no significant difference between Group I and Group II in the amount of actual mediastinal blood loss, in units of whole blood transfused, or in units of packed cells transfused (Table III). There was only one reoperation (in Group I) during which a bleeding side branch of a vein graft was found and ligated. No overt coagulopathies developed in either group.

Discussion

Cardiac surgeons have long sought ways to minimize the coagulopathy caused by operations that employ extracorporeal circulation. Frequently cited causes include thrombocytopenia,[1,3,4,8] fibrinolysis,[1,8] subtle alterations in plasma clotting factors,[8] incorrect heparin reversal,[1,9] cyanotic heart disease,[1,4] prolonged bypass times[1,3] and, occasionally, a history of prior cardiac surgery.[10] Although biochemical abnormalities are frequently detected at the completion of bypass, these abnormalities rarely result in clinically significant bleeding and rapidly return to normal with or without treatment.[1,8]

The assessment of whether or not to treat these biochemical abnormalities must take into account the specific causes of the disorder, the ability of the proposed remedy to modify these causal forces, the risks inherent in the treatment, and the end-result of the treatment; that is, whether patients are significantly improved by the remedy.

Platelet counts regularly diminish with the onset

TABLE III
Blood Loss and Transfusion Requirements

	Group I	Group II	Significance
Reoperation	1	0	NS
Whole Blood	2.95 ± 1.72 units	3.04 ± 1.34 units	NS
Packed Cells	3.00 ± 1.68 units	2.68 ± 1.67 units	NS
Chest Drainage—1	676 ± 449 cc.	531 ± 286 cc.	NS
Chest Drainage—2	200 ± 120 cc.	211 ± 155 cc.	NS

NS = Not significant ($p > 0.05$)

of extracorporeal circulation, although unless the thrombocytopenia is severe, overt hemorrhage is unusual. In any event the specific treatment for this disorder is platelet transfusion, not FFP.

Fibrinolysis has been implicated frequently as a major cause of postbypass bleeding. A shortening of the euglobulin lysis time may be found in up to 50 per cent of the patients undergoing cardiopulmonary bypass, but only a small number of patients have clinically significant hemorrhage.[1,3,4,12,13] Increased plasminogen activator levels have been detected, not only after bypass, but also after thoracotomy or sternotomy itself,[3,4] so the significance of these abnormalities in the post-bypass period is unclear. The lytic activity disappears spontaneously with or without specific therapy in the majority of cases after the heparin is neutralized with Protamine.[8] The specific treatment for a well-documented fibrinolytic syndrome is epsilon aminocaproic acid (EACA) but its prophylactic administration is discouraged unless there is adequate proof that a true lytic state exists.[3] The indiscriminate use of EACA can worsen hemorrhage in selected instances when true intravascular coagulation is present rather than fibrinolysis. However, since no antifibrinolytic activity is present in FFP, its prophylactic use in the post-bypass patient is not recommended for correction of a prolonged euglobulin lysis time.

Although abnormalities in prothrombin time and partial thromboplastin time are often found after cardiopulmonary bypass, their significance is uncertain. There is a wide range of normal values and generally a lack of correlation between the laboratory results and the presence of significant hemorrhage.[5]

Fibrinogen levels decline at the outset of bypass and another decline often follows the reversal of heparin by protamine.[14] The defibrination is thought to be caused by a subtle clotting phenomenon which consumes coagulation factors after heparin reversal is over-corrected with protamine. This has been labelled permissive defibrination.[14] Although the authors[14] indicated that omission of heparin reversal might obviate this finding, it seems more appropriate that more accurate reversal of heparin activity should be accomplished so that neither a hyper- nor a hypocoagulable state is permitted. Use of the activated clotting time (ACT) back-calculations to determine accurately the levels of circulating heparin and, therefore, appropriate protamine dosages has, we believe, prevented some of the abnormalities of hemostasis that were previously noted after "blind" protamine reversal.[7]

The administration of FFP will augment the plasma clotting factors, but because the clinical significance of the biochemical alterations seen after bypass is difficult to assess, one cannot easily show a beneficial effect. Kaplan et al.[15] administered three units of FFP as well as eight units of platelets "prophylactically" at the end of bypass and found that the prothrombin time, the partial thromboplastin time and the platelet count were improved in the group receiving FFP and platelets but that there was no difference in postoperative blood loss between the study group and those who did not receive FFP. Thurer et al.[9] found that, despite the lack of component therapy and despite the biochemical abnormalities in the hemogram, excessive bleeding did not occur. The "therapeutic nonspecificity and inappropriateness"[9] of the routine use of blood components have been previously discouraged and our data supports this view. No measurable difference could be found between Groups I and II with respect to routinely measured clotting parameters, postoperation mediastinal drainage, or banked blood requirements.

Our patients were adults, the majority of whom underwent coronary bypass grafting and were on bypass for relatively short times at moderate hypothermia. Children with cyanotic heart disease are more prone to postoperative coagulopathies.[1,4] Since the duration of extracorporeal circulation has an effect on the extent of alterations on blood proteins and hence coagulation factors, it may well be that procedures for the correction of cyanotic heart disease, and those which require prolonged bypass times and greater degrees of hypothermia would yield different results, and this should be the subject of further study.

The routine use of FFP carries certain disadvantages, including risks of infection, added cost ($40/unit in our institution), a strain on blood bank resources and risks of isoimmunization reactions. Since no benefit can be demonstrated in terms of reducing homologous blood requirements or mediastinal drainage, nor does its use improve

routinely measured clotting parameters, the administration of FFP following routine cardiopulmonary bypass should be discouraged.

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