

Failure of Prophylaxis with Fresh Frozen Plasma after Cardiopulmonary Bypass

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Despite the recommendations of the 1984 Consensus Conference,¹ many clinicians still administer fresh frozen plasma (FFP) prophylactically after cardiopulmonary bypass to offset the dilution of clotting factors.²⁻⁶ The risks of disease transmission^{6,7} and noncardiogenic pulmonary edema (NCPE)⁷⁻⁹ from FFP mandate clear documentation of its benefit to justify its routine prophylactic use. We had the opportunity to study its efficacy when a cardiac anesthesia and surgical team, previously using liberal amounts of FFP in their fluid administration protocol, eliminated it completely from their regimen after a patient developed NCPE during an infusion of FFP. We present a sequential retrospective study of blood product administration, coagulation profiles, and blood loss in 100 patients presenting for coronary artery bypass surgery who received either FFP or albumin after cardiopulmonary bypass.

MATERIALS AND METHODS

We reviewed the anesthetic and intensive care unit (ICU) records of 100 consecutive patients who had undergone elective aortocoronary artery bypass grafting by the same surgeon between August, 1984, and March, 1985. Fifty-two patients received FFP post-bypass (group F), and 48, treated after the episode of NCPE, received albumin (group A). Preoperatively, all patients had normal prothrombin (PT), activated par-

tial thromboplastin (PTT), and bleeding times, normal platelet counts, and hemoglobins greater than 12 g/dl. None were taking aspirin in the 2 weeks prior to surgery.

All patients were premedicated with im morphine and oral lorazepam, and were anesthetized with iv fentanyl or sufentanil supplemented with diazepam or low concentrations of halothane, enflurane, or isoflurane. Six anesthesiologists were involved. All patients underwent nonpulsatile cardiopulmonary bypass with Shiley S100A bubble oxygenators, crystalloid prime, moderate hypothermia, and cold potassium cardioplegia. Systemic heparinization, achieved with 400 u/kg, was monitored using the activated clotting time (ACT) (Hemochron, International Technidyne, Inc., Edison, NJ) and an automated heparin-protamine titration (Hepcon System A-10, HemoTec, Inc., Englewood, CO).¹⁰ During bypass, the ACTs always exceeded 480 s and the circulating heparin always exceeded 250 u/kg. The protamine dose was also determined by heparin-protamine titration. The protamine was administered intra-aortically as previously described.¹¹ The return of serial ACTs to normal and the absence of a heparin effect in the protamine titration confirmed heparin neutralization.

The surgical team salvaged blood from the operative field only during anticoagulation. No cell-saving device was utilized, nor was residual blood in the oxygenator transfused after removal of the aortic cannula. No patient had internal mammary artery anastomoses with thoracotomy drains. Those patients with hematocrits less than 32% requiring volume were transfused with bank blood. Blood from mediastinal drainage was not processed and reinfused.

Group F patients received two units of FFP after confirmation of heparin neutralization with protamine. Additional units were given for volume replacement as indicated by the systemic and pulmonary capillary wedge pressures. Patients in group A, given no FFP, received 5% albumin for volume replacement. PT and PTT determinations proceeded immediately upon arrival of the patient in the ICU. Blood loss was defined as the 24-h mediastinal drainage volume.

The two groups were compared using Student's *t* test for the parametric data, the Mann-Whitney U-test for the non-parametric data, and the Chi-square test for the sex ratios and the distribution of anesthesiologists.

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RESULTS

Between the two groups, no differences existed in age, number of grafts, bypass time, heparin and protamine doses, male:female ratio, or distribution of anesthesiologists. The PT was shorter, but the PTT was longer, in group F ($P < 0.05$). One patient in group F and two patients in group A required re-exploration for bleeding, and were not included in the data presented in tables 1 and 2. In these three patients, bleeding was confined to specific sites with no observation of generalized bleeding. The 24-h blood losses were less than 1100 ml in all remaining patients, except for two in group F (table 1). These two patients account for the larger mean blood loss in group F, although the difference in blood loss between the two groups was not statistically significant. Also, the administration of platelets to these two patients allowed the difference between groups in the number of units of platelets transfused to achieve significance.

Between the two groups, the number of units of whole blood and packed red cells transfused did not differ (table 2). However, the patients in group F received more blood components due to the highly significant ($P < 0.001$) difference in the number of FFP units given to these patients for bleeding prophylaxis and intravascular volume replacement.

DISCUSSION

Our results suggest that the prophylactic administration of an average of six units of FFP does not reduce blood loss or limit the number of patients requiring re-exploration for bleeding after cardiopulmonary bypass. Kaplan *et al.* previously demonstrated that the prophylactic administration of two units of FFP and eight units of platelets did not improve 24-h blood loss.¹² In both studies, higher hematocrits were sought than is now more commonly the case.^{13,14} The results of these studies would be more relevant to current practice if more hemodilution and blood conservation had been practiced. Each unit of red cells or platelets contains 50–75 ml of plasma; each unit of whole blood, 250–300 ml of plasma.¹⁵ Factors V and VIII are more stable in this plasma than previously thought.^{16,17} Enough plasma may have been present in the bank blood products administered to the albumin and control groups in the above studies to restore clotting factors to levels above the threshold required for a normal hemostatic response,¹⁶ if, indeed, they ever did fall below that threshold.^{4,18–20} Thus, the contribution that FFP may have made would have to be determined by direct factor assays.

The prophylactic administration of FFP does not appear to be necessary for at least three reasons. First,

TABLE 1. Units of Various Blood Components Transfused and Number of Blood Component Donors

	Group F (FFP)	Group A (Albumin)
Blood components, units		
Whole blood	1.5 ± 0.2 (0–4)	1.8 ± 0.2 (0–4)
Total blood	5.5 ± 0.3 (2–10)	5.3 ± 0.2 (3–10)
Platelets	2.7 ± 0.8 (0–24)	0.9 ± 0.4* (0–12)
Fresh frozen plasma	5.8 ± 0.5 (2–16)	0.2 ± 0.1† (0–2)
Donors per patients	14.0 ± 0.5	6.4 ± 0.5†

Total blood = whole blood + packed red cells; platelets = random donors; all values expressed as mean ± SEM (range).

* $P < 0.05$.

† $P < 0.001$.

although dilution of clotting factors does occur, the post-bypass plasma levels of all clotting factors remain more than adequate for normal hemostasis, and rapidly recover to pre-bypass levels.^{4,18–20} Second, body stores and *de novo* synthesis of coagulation proteins by the liver create a reserve which, for example, is sufficient to maintain clotting activity at an effective level, even after extensive plasmapheresis.²¹ Although effective hepatic blood flow suffers a reduction during non-pulsatile cardiopulmonary bypass, it returns to normal within 30 min after resumption of pulsatile flow.^{22,23} Even in liver transplant patients, the transplanted liver makes clotting factors within a short time after its implantation.²⁴ Finally, and most importantly, platelet dysfunction, not coagulation protein deficiency, appears to be the most likely cause of bleeding problems after bypass.^{18,25–27}

The longer PTT in the FFP group may indicate a small residual heparin effect. FFP prolongs the ACT in heparinized patients with normal antithrombin III levels.²⁸ Shanberge *et al.* have demonstrated *in vitro* that

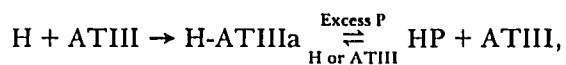
TABLE 2. Blood Loss and Coagulation Studies

	Group F (FFP)	Group A (Albumin)
Re-explored	1	2
Significant bleed	2	0
Blood loss (ml)	630 ± 44 (245–1700)	550 ± 24 (250–950)
PT (s)	14.6 ± 0.1 (12.6–17.9)	15.2 ± 0.1* (13.8–18.1)
PTT (s)	31.6 ± 0.8 (25.2–59.1)	29.7 ± 0.5* (22.7–39.8)

PT = prothrombin time (normal 11.0–13.4 s), PTT = partial thromboplastin time (normal < 31 s), both determined on arrival in ICU from OR; significant bleed = total ml blood loss > 1100 ml, but < 300 ml/h. Values expressed as mean ± SEM (range).

* $P < 0.05$.

FFP reverses protamine neutralization of heparin. The antithrombin III in the FFP shifts the heparin neutralization reaction to the left by the law of mass action:



where H = heparin; ATIII = antithrombin III; ATIIIa = active antithrombin III; and HP = heparin-protamine complex.²⁹ More protamine would then be required.

Since FFP does not appear to contribute measurably to post-bypass hemostasis, it becomes primarily a colloid volume expander, performing a function that can be better assumed by more innocuous therapeutic agents. Plasma substitutes are associated with no disease transmission and fewer untoward reactions.³⁰⁻³² Although 5% albumin, used in place of FFP in this study, technically represents a blood component, the process of cold ethanol fractionation and subsequent heat treatment effectively sterilize it.^{31,33} Also, it contains no immunoglobulins to trigger NCPE. The incidence of life-threatening reactions relating to albumin administration is only 0.003%, whereas the incidence climbs to 0.1% for FFP.^{30,32}

The sequential nature of this study (*i.e.*, one group examined, then another) does represent a major shortcoming. However, limiting the study to a single surgical team performing the same procedure over a limited time span offsets the disadvantages of some prospective studies, which usually involve several surgeons using different fluid regimens and heparin and protamine protocols. Because the decision to perform the chart review came as a result of the adverse publicity FFP was receiving³⁴ and after the surgeries had been performed, the study did not influence surgical technique.

A separate issue is whether the administration of FFP is indicated in those patients who still seem to be bleeding after heparin neutralization. In a recent study designed to demonstrate cost-effectiveness of blood conservation, FFP was administered to 20% of 284 patients without documentation of a fall in factor levels below critical concentrations.¹⁴ This practice is commonplace.^{2,3} There are no studies that document the efficacy of FFP in this setting, nor are they likely to be any. FFP infused at a rate of at least 800 ml/70 kg/h improved factor levels only marginally and temporarily in the presence of hemorrhagic shock in humans.¹⁶ Large doses of FFP did not restore coagulation activity in a well-designed dog study of hemorrhagic shock by Martin *et al.*³⁵

In summary, a case of NCPE, temporally associated with the prophylactic administration of FFP to a patient after cardiopulmonary bypass, prompted re-evaluation of FFPs contribution toward the reduction of bleeding problems. No difference existed in blood loss or in units

of blood transfused when comparing patients receiving FFP prophylactically after cardiopulmonary bypass with those receiving 5% albumin. Substitution of the albumin for FFP permitted a reduction in the number of stored blood products and reduces the risk of disease transmission or untoward reaction. Blood conservation methods, which decrease the homologous blood requirement, would further reduce these risks.

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Rise in Pulmonary Arterial Pressure following Release of Aortic Crossclamp in Abdominal Aortic Aneurysmectomy

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Many reports¹⁻⁶ have described the hemodynamic effects of aortic cross-clamping (XC) and declamping (XD) during surgery for abdominal aortic aneurysms

(AAA). Although systemic arterial hypotension following XD is well established, reports of changes in pulmonary arterial pressure are not well documented. During routine monitoring of patients during AAA surgery, we noted a transient rise in pulmonary arterial pressure (PAP) following XD. We, therefore, prospectively evaluated changes in pulmonary arterial pressure after XD in patients undergoing AAA surgery.

MATERIALS AND METHODS

Eighteen consecutive patients (NYHA Class I or II) undergoing elective surgical treatment of infrarenal AAA were selected for study after institutional approval and informed consent were obtained. Five patients were excluded from the results (*vide infra*). The

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Key words: Lung; pulmonary hypertension. Monitoring: end-expiratory carbon dioxide; mixed venous oxygen saturation; pulmonary arterial pressure. Surgery: aortic aneurysmectomy; aortic cross-clamping; aortic declamping.