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Failure of Autologous Fresh Frozen Plasma to Reduce Blood Loss and Transfusion Requirements in Coronary Artery Bypass Surgery

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Background: **Previous studies failed to demonstrate any benefit from prophylaxis with fresh frozen plasma (FFP) after cardiopulmonary bypass (CPB). The results, however, were limited by either retrospective study design or use of FFP in subtherapeutic doses (2–3 units). The authors evaluated whether a therapeutic dose (15 ml/kg) of FFP reduces blood loss and transfusion requirements in elective coronary artery bypass surgery. The risks of multiple allogeneic blood donor exposure were circumvented by using autologous plasma.**

Methods: **Sixty adult patients scheduled for elective primary coronary artery bypass grafting were randomized to receive, after CPB, an intravenous infusion of 15 ml/kg of either autologous FFP (30 patients) or 6% hydroxyethyl starch 450/0.7 (HES; 30 patients). Autologous plasma was obtained by platelet-poor plasmapheresis several weeks before surgery. Perioperative blood transfusions were administered per protocol. Postoperative blood loss was defined as the chest tube drainage during the first 24 h after surgery.**

Results: **The data from 56 patients (FFP group, 27 patients; HES group, 29 patients) who completed the study according to protocol were analyzed. Median postoperative blood loss was 630 ml (range, 450–1,840 ml) and 830 ml (range, 340–1,980 ml) in the FFP and HES groups, respectively ($P = 0.08$). Both postoperative (0–24 h) and total perioperative erythrocyte transfusion requirements did not differ significantly between the groups ($P = 0.32$ and 0.14, respectively).**

Conclusion: **The prophylactic administration of a therapeutic dose (15 ml/kg) of autologous FFP after CPB failed to reduce blood loss and transfusion requirements in patients undergoing uncomplicated, elective, primary coronary artery bypass surgery.**

THE use of fresh frozen plasma (FFP) in coronary artery bypass surgery is subject to marked interhospital variability, which is accounted for, in part, by prophylactic and inappropriate plasma transfusion.[1–3] Audits of transfusion practice in elective coronary artery bypass surgery revealed that the percentage of patients transfused with FFP varied between 0% and 100% among institutions,[4–6] with transfusion frequencies greater than 20%, suggesting inappropriate plasma transfusion practice. Previous studies failed to demonstrate a reduction of blood loss and blood use by the prophylactic use of FFP after cardiopulmonary bypass (CPB), but were flawed by either retrospective study design[7] or use of FFP in doses too small (2–3 units) for being effective in the treatment of hemostatic disorders.[8–10] One reason for using subtherapeutic doses of FFP in previous trials could have been the risks associated with multiple allogeneic blood donor exposure, such as virus transmission, alloimmunization, and anaphylactoid reactions.[3] We designed a controlled, randomized trial to test the hypothesis that a therapeutic dose (15 ml/kg)[11–13] of FFP reduces blood loss and transfusion requirements in elective coronary artery bypass surgery. The risks of multiple allogeneic blood donor exposure were circumvented by using autologous FFP.

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Materials and Methods

After obtaining approval of the study from the Ethics Committee of the Medical Faculty of the University of Cologne (Cologne, Germany), 60 adult patients scheduled for elective primary coronary artery bypass grafting gave written, informed consent for their participation. Patients were included in the study if they were on the hospital's waiting list for elective coronary artery bypass grafting, had an anticipated waiting period of 4 weeks or more, weighed between 50 and 100 kg, and met established selection criteria for autologous blood donors.[14] Exclusion criteria were left ventricular ejection fraction less than 40%, hemoglobin concentration less than 12 g/dl, total plasma protein concentration less than 60 g/l, recent (< 7 days) or current medication with any drugs known to affect blood coagulation, abnormal blood coagulation test results (prothrombin time [Quick value] < 70%, activated partial thromboplastin time > 40 s, fibrinogen concentration < 1 g/l, platelet count $< 150 \times 10^9$/l), plasma creatinine concentration greater than 1.5 mg/dl, and known allergy against hydroxyethyl starch (HES).

Potential candidates were contacted by letter and provided with preliminary information about the study. Interested patients were requested to make an appointment for a screening examination. After they had given

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written, informed consent, eligible patients were randomly allocated to either an FFP group or a HES group. Randomization was based on a computer-generated code that was prepared by an individual not involved in the study and was sealed in sequentially numbered, opaque envelopes. Patients in the FFP group had a total volume of 15 ml/kg of autologous, platelet-poor plasma collected at two visits during the preoperative period, which was reinfused intraoperatively after termination of CPB and heparin neutralization. Patients in the HES group did not donate autologous plasma before surgery and received, at the corresponding time, an intravenous infusion of 15 ml/kg hetastarch (6% HES; mean molecular weight, 450 kd; degree of substitution, 0.7; Plasmasteril, Fresenius AG, Bad Homburg, Germany). No patient in either group donated erythrocytes for autologous use during surgery.

Autologous plasma in the FFP group was collected by plasmapheresis. We used the Organon Teknika Plasmapur system (Organon Teknika Medizinische Produkte GmbH, Eppelheim, Germany) to obtain 7 and 8 ml/kg of autologous platelet-poor plasma, respectively, at two visits separated by an interval of 7–10 days. At least 1 week elapsed between the last visit and surgery. Whole blood was withdrawn from a cubital vein into a sterile, closed-circuit tubing set, anticoagulated with acid-citrate-dextrose solution in a 12:1 ratio, and separated into corpuscular elements and platelet-poor plasma by hollow-fiber filtration.[15] During the procedure, which took approximately 1 h, the corpuscular elements intermittently were returned to the patient. Concurrently, 10 ml/kg of lactated Ringer solution was infused into a vein of the contralateral arm to maintain intravascular volume. Plasma was shock-frozen at −80°C within 2 h of collection and then stored at −30°C until reinfusion (< 2 months in all cases). The quality of the plasma was checked by determinations of the activity of the coagulation factor VIII:C in 10 random samples after thawing (*i.e.*, before reinfusion). The activity of the coagulation factor VIII:C was determined by one-stage assay.[16]

All patients received a standard anesthetic consisting of intravenous fentanyl, midazolam, and pancuronium in body weight–related doses. After intubation of the trachea, the lungs were ventilated with 50% oxygen in air using a semiopen circle system. Tidal volume and ventilatory rate were adjusted to keep the arterial carbon dioxide partial pressure between 36 and 44 mmHg, except during total CPB. No patient received aprotinin or any other antifibrinolytic agent. Patients were anticoagulated with porcine heparin at an initial dose of 300 IU/kg, injected intravenously before cannulation of the aorta. Additional heparin was administered when the celite activated clotting time was less than 450 s. CPB was accomplished with a nonocclusive roller pump and a membrane oxygenator (Cobe Duo, Cobe Cardiovascular, Inc., Arvada, CO). The circuit was primed with 2,000 ml lactated Ringer solution, 50 mM sodium bicarbonate, and 2,000 IU heparin. Pump flow was maintained at 2.4 $l \cdot min^{-1} \cdot m^{-2}$ during moderate hypothermia (urinary bladder temperature > 28°C). Cardiac arrest was induced with 20 ml/kg cold crystalloid cardioplegia (Bretschneider solution, Custodiol, Dr. Franz Köhler Chemie GmbH, Alsbach-Hähnlein, Germany). Lactated Ringer solution was added to the CPB circuit to maintain filling volume when needed. Packed erythrocytes were added when the hemoglobin concentration was less than 7 g/dl. After rewarming the patient to 37°C and discontinuation of CPB, 60% of the cumulative heparin dose was neutralized by intravenous infusion of protamine hydrochloride. Heparin neutralization was regarded as adequate if the postprotamine activated clotting time value was within 10% of the preheparin value. Increments of protamine were administered if the activated clotting time did not return to within 10% of baseline after the calculated dose. The residual blood in the CPB circuit was processed through a blood salvage device (Cell Saver IV, Haemonetics GmbH, Munich, Germany), with the erythrocytes returned in all cases.

After adequate heparin neutralization was confirmed, patients received an intravenous infusion of 15 ml/kg of either autologous, platelet-poor plasma (FFP group, 30 patients) or hetastarch (HES group, 30 patients). The investigators were not blinded to which substance was being administered. Plasma was thawed at 37°C by a microwave device immediately before infusion. The infusions were completed within 60 min in all patients. Postoperatively, patients were transferred to the intensive care unit (ICU), and their lungs were mechanically ventilated until patients were hemodynamically stable and no major bleeding was noted. Major bleeding was defined as chest tube drainage greater than 200 ml/h for 2 consecutive hours. Fluid therapy in the ICU consisted of a basic crystalloid infusion (40–60 ml/h) and infusion of 5% human serum albumin when the central venous pressure decreased to less than 10 mmHg. Packed erythrocytes were transfused when the hemoglobin concentration was less than 9 g/dl. Allogeneic FFP and platelet concentrates, respectively, were transfused for correction of microvascular bleeding (chest tube drainage > 200 ml/h for 2 consecutive hours) in the presence of abnormal blood coagulation values (Quick value < 40%, activated partial thromboplastin time > 60 s, fibrinogen concentration < 1 g/l, platelet count < 50×10^9/l).[13,17]

Chest tube drainage volume was recorded until 24 h postoperatively. After the first 6 h, a sample of the drainage fluid was collected for measurement of the hematocrit. Blood use was recorded until postoperative day 7. Blood samples for laboratory studies were drawn before the induction of anesthesia (baseline), after completion of the infusions of autologous, platelet-poor plasma or HES (on arrival in the ICU), 24 h after arrival in the ICU, and on postoperative days 3 and 7. Blood

samples at baseline and on postoperative day 7 were obtained by venipuncture. Blood samples at the other times were drawn from a central venous catheter after flushing with normal saline and discarding the first 10 ml of the aspirated blood (approximately five times the dead space of the system). Laboratory variables included hemoglobin concentration, platelet count, prothrombin time (Quick value), activated partial thromboplastin time, and plasma concentrations of fibrinogen, antithrombin III, and albumin. Variables were determined by standard laboratory methods.

Statistical Analysis

The primary outcome variable was postoperative blood loss, which was defined as the chest tube drainage during the first 24 h after surgery. Based on unpublished data from our institution (indicating an SD for the 24-h chest tube output of 350 ml), we estimated that a sample size of 42 patients (21 patients per group) was required to detect, with 90% power at the 0.05 significance level, a 250-ml difference in chest tube drainage between the two groups. Assuming a hematocrit of the drainage fluid of approximately 25%,[18–20] 250 ml of chest tube drainage contains approximately 60 ml erythrocytes, or approximately one third of the erythrocyte mass (200 ml) of a typical unit of packed erythrocytes.[21] A difference less than this was considered unlikely to be clinically important.

Results are reported as mean ± SD and median (range) for parametric and nonparametric data, respectively. Patient characteristics and data related to the surgical procedure were compared by Student *t* test. Laboratory variables were compared by repeated-measures analysis of variance followed by Scheffé test for *post hoc* comparisons between groups. Chest tube drainage volume, the hematocrit of the drainage fluid, and perioperative blood use were compared using the Mann–Whitney U test. Proportions were compared by Fisher exact test. All tests were two-sided, with $P < 0.05$ considered significant.

Results

Sixty patients were enrolled in the study, and 56 patients (FFP group, 27 patients; HES group, 29 patients) completed it according to protocol. Four patients (FFP group, 3 patients; HES group, 1 patient) were excluded from analysis: one patient from each group developed severe left ventricular failure during weaning from CPB and required intraaortic balloon pumping; the infusion of a relatively large quantity (15 ml/kg) of fluid within a short period of time was deemed inappropriate in these patients. Two patients in the FFP group required reexploration for bleeding, which was confined to specific sites with no observation of generalized bleeding.

Table 1. Patients and Procedures

	FFP (n = 27)	HES (n = 29)
Male:Female ratio	24:3	25:4
Age (yr)	58 ± 7	56 ± 8
Weight (kg)	77 ± 9	74 ± 7
Number of bypass grafts	2.6 ± 0.9	2.6 ± 0.8
Patients receiving LIMA grafts (n)	21	22
Duration of surgery (min)	248 ± 66	246 ± 51
Cardiopulmonary bypass time (min)	77 ± 9	74 ± 7
Cross-clamp time (min)	44 ± 15	51 ± 16
ACT before heparin (s)	127 ± 23	133 ± 26
ACT after protamine (s)	130 ± 22	126 ± 16
Intraoperative blood salvage (ml)	695 ± 213	736 ± 226
Temperature at arrival in the ICU (°C)	35.8 ± 0.7	35.4 ± 0.7

Values are expressed as mean ± SD.

FFP = autologous fresh frozen plasma; HES = hydroxyethyl starch; n = number of patients; LIMA = left internal mammary artery; ACT = activated clotting time; ICU = intensive care unit.

There was no significant difference between the two groups with respect to demographic data and surgical procedure (table 1). Baseline laboratory variables also were not significantly different between the two groups (table 2). Blood coagulation test results at baseline were normal in all patients.

After CPB and heparin neutralization, patients in the FFP group received 1,161 ± 129 ml autologous, platelet-poor plasma; patients in the HES group received 1,123 ± 106 ml hetastarch. Coagulation factor VIII:C concentrations (0.9 ± 0.12 IU/ml) in random samples of the thawed plasma met the required standard (> 0.7 IU/ml)[22] in all cases.

Chest tube drainage during the first 24 h after surgery ranged from 450 to 1,840 ml in the FFP group and from 340 to 1,980 ml in the HES group (difference between medians: 200 ml, $P = 0.08$; table 3). The hematocrit of the drainage fluid, as measured in samples collected after the first 6 h, was similar for both groups (FFP group: 17% [range, 7–30%], HES group: 19% [range, 8–27%]; $P = 0.53$). One patient in the FFP group and five patients in the HES group had a 24-h chest tube output greater than 1,200 ml ($P = 0.19$).

Perioperative blood use was not significantly different between the two groups. In addition to the transfusion of packed erythrocytes (table 3), three patients in the HES group postoperatively received a total of 7 units of FFP (two patients, 2 units; one patient, 3 units). The indications were plasma fibrinogen concentration less than 1 g/l (two patients) and activated partial thromboplastin time greater than 60 s (one patient) in the presence of microvascular bleeding. One patient from each group received 2 units of platelet concentrate for a laboratory platelet count less than 50×10^9/l in the presence of microvascular bleeding. Overall, 21 of the 27 patients in the FFP group received at least one unit of allogeneic blood (packed erythrocytes, FFP, platelets)

Table 2. Laboratory Variables

Variable	Baseline	After FFP or HES	24 h ICU	POD 3	POD 7
Hemoglobin (g/dl)					
FFP	13.4 ± 1.0	8.5 ± 1.3	10.1 ± 0.9	10.9 ± 1.2	11.2 ± 1.7
HES	13.5 ± 1.2	8.7 ± 1.4	10.1 ± 1.0	11.8 ± 1.5	11.6 ± 1.5
Platelet count ($\times 10^9$/l)					
FFP	189 ± 52	109 ± 36	116 ± 61	230 ± 118	448 ± 139
HES	213 ± 60	101 ± 44	117 ± 41	194 ± 67	492 ± 160
Prothrombin time (Quick value) (%)					
FFP	77 ± 11	58 ± 10*	69 ± 10	85 ± 11	75 ± 18
HES	79 ± 9	46 ± 8	63 ± 13	82 ± 9	79 ± 12
aPTT (s)					
FFP	29 ± 9	40 ± 6*	36 ± 8	27 ± 6	28 ± 9
HES	25 ± 3	48 ± 9	38 ± 9	26 ± 3	25 ± 4
Fibrinogen (g/l)					
FFP	2.7 ± 0.6	1.8 ± 0.5*	3.4 ± 0.8	5.3 ± 1.2	4.4 ± 0.5
HES	2.9 ± 0.6	1.3 ± 0.4	2.9 ± 0.8	4.8 ± 0.8	4.7 ± 0.9
Antithrombin III (%)					
FFP	73 ± 9	58 ± 15*	56 ± 11	69 ± 10	87 ± 15
HES	77 ± 12	40 ± 10	53 ± 11	74 ± 10	84 ± 14
Plasma albumin (g/l)					
FFP	39 ± 4	34 ± 5*	45 ± 4	44 ± 5	40 ± 5
HES	38 ± 4	25 ± 4	40 ± 4	38 ± 4	39 ± 3

Values are expressed as mean ± SD. Normal ranges: hemoglobin, males: 13.5–18 g/dl, females: 12–16 g/dl; platelet count: 150–400 $\times$ 10^9/l; prothrombin time (Quick value): 70–120%; activated partial thromboplastin time (aPTT): ≤ 38 s; fibrinogen: 1.8–3.5 g/l; antithrombin III: 70–120%; plasma albumin: 35–52 g/l.

* $P < 0.05$ *versus* HES group.

FFP = autologous fresh frozen plasma; HES = hydroxyethyl starch; baseline = before induction of anesthesia; after FFP or HES = after infusion of 15 ml/kg FFP (27 patients) or HES (29 patients); 24 h ICU = 24 h after arrival in the intensive care unit (ICU); POD = postoperative day.

compared with 23 of the 29 patients in the HES group ($P = 1.0$). The average number of allogeneic blood units per patient did not differ between the two groups (FFP group: median, 2 units [range, 0–11 units]; HES group: median, 3 units [range, 0–10 units]; $P = 0.13$).

On arrival in the ICU (*i.e.*, after the infusion of autologous, platelet-poor plasma or hetastarch), patients in the FFP group had blood coagulation test results that were closer to normal than those of the patients in the HES group (table 2). Blood coagulation values did not differ between the two groups 24 h after arrival in the ICU and on postoperative days 3 and 7.

Discussion

We found that the prophylactic administration of a therapeutic dose (15 ml/kg) of FFP after CPB did not reduce blood loss and transfusion requirements in uncomplicated, elective, primary coronary artery bypass surgery. This finding is consistent with the results of previous studies of the effects of prophylaxis with FFP in cardiac surgery.[7–10] However, the conclusions that could be drawn from these studies were limited by either shortcomings in study design[7] or use of FFP in subtherapeutic doses (2–3 units).[8–10] The recommended initial

Table 3. Chest Tube Drainage and Erythrocyte Transfusion

	FFP (n = 27)	HES (n = 29)	*P* Value
Chest tube drainage (ml)			
0–12 h postoperative	380 (250–1160)	430 (180–1250)	0.35
0–24 h postoperative	630 (450–1840)	830 (340–1980)	0.08
Erythrocyte transfusion (units)			
intraoperative*	0 (0–5)	0 (0–3)	0.50
postoperative (0–24 h)	1 (0–3)	2 (0–5)	0.32
perioperative†	2 (0–11)	3 (0–6)	0.14
Patients receiving ≥ 1 unit erythrocytes			
intraoperative	8	11	0.74
postoperative (0–24 h)	20	22	1.0
perioperative	21	23	1.0

Values are expressed as median (range).

FFP = autologous fresh frozen plasma; HES = hydroxyethyl starch; n = number of patients.

* Not including intraoperative salvage. † Includes all banked erythrocyte transfusions from the start of surgery until postoperative day 7.

dose of FFP for the treatment of coagulation defects ranges between 10 and 15 ml/kg, *i.e.*, between 800 and 1,200 ml (4–6 units) for an 80-kg patient.[11–13,23]

Several reasons may explain the lack of a demonstrable benefit from the routine use of FFP after CPB. First, the magnitude of the decrease in plasma levels of coagulation factors during CPB is usually not sufficient to cause abnormal bleeding.[24] Second, the postbypass plasma levels of coagulation proteins rapidly recover to prebypass levels in most patients. Possible mechanisms include hemoconcentration, equilibration with extravascular compartments, and *de novo* synthesis of coagulation proteins in the liver.[25,26] Finally, and most importantly, bleeding after CPB is most often caused by platelet dysfunction and not depletion of coagulation proteins.[24] Prevention of abnormal (nonsurgical) bleeding after CPB should thus primarily aim at improving platelet function.[27]

We are aware of one previous study of the use of autologous platelet-poor plasma in coronary artery bypass surgery.[28] In that study, 10 ml/kg autologous platelet-poor plasma was collected after the induction of anesthesia, stored at room temperature, and returned after CPB. The chest tube drainage in the autologous plasma group was significantly reduced compared with the drainage volume in a control group of patients who were not subjected to plasmapheresis (543 ± 230 ml *vs.* 696 ± 130 ml, $P < 0.05$). No explanation was found for this difference, with the exception of higher postoperative plasma concentrations of fibrinogen and antithrombin III in the autologous plasma group. However, plasma levels of all coagulation factors were not reduced to critical levels in the control group, and no significant difference in blood coagulation was observed between the groups on the thromboelastogram. In our study, as in the study by Boldt *et al.*,[28] postoperative plasma concentrations of fibrinogen and antithrombin III likewise were higher in the FFP group than the HES group, but this did not translate into a reduction in postoperative blood loss or transfusion requirements.

Some aspects of our study deserve discussion. To circumvent the risks associated with multiple allogeneic blood donor exposure (*e.g.*, virus transmission, alloimmunization, anaphylactoid reactions),[3,29] we used autologous FFP instead of allogeneic FFP. One might be concerned that the quality of the autologous plasma was inferior to that of allogeneic FFP. However, apart from their cardiovascular status, all patients in our study met the same selection criteria as apply for allogeneic plasma donors,[22] plasma was collected, stored, and thawed according to established standards,[30] and adequate retention of coagulation factors was confirmed by high levels (> 0.7 IU/ml) of the activity of the labile coagulation factor VIII:C in random samples of the thawed plasma.

The median difference between the 24-h chest tube drainage in the FFP group and the HES group was 200 ml. Although the *P* value (0.08) suggests that, in a study with a larger patient population, this difference might have reached significance, a 200-ml difference in chest tube output is unlikely to be clinically important. Given an average hematocrit of the drainage fluid of approximately 20%, as was found in our study, 200 ml of drainage fluid contains approximately 40 ml of erythrocytes, or one fifth the erythrocyte mass of a unit of packed erythrocytes.[21] In our *a priori* power analysis, 250 ml of chest tube drainage, or 60 ml of erythrocytes, was accepted as the smallest difference that would be clinically important. In addition, the use of hetastarch (6% HES 450/0.7) and the abstention from prophylaxis with antifibrinolytic agents such as aprotinin and ε-aminocaproic acid might have biased our results in favor of the FFP group. There is evidence that the use hetastarch and abstention from using antifibrinolytic drugs increase blood loss and transfusion requirements in cardiac surgery.[31,32] This may have increased the chance of finding an effect of FFP on postoperative blood loss in our study, which was not present, however. In this context, it is noteworthy that during the first 12 h in the ICU, when the effects of the infusion of the autologous plasma should have been most pronounced, median chest tube output differed no more than 50 ml between the FFP and HES groups.

The unblinded nature of our study is a possible limitation. We refrained from blinding this study because we expected that the blood coagulation test results (which the attending physicians needed to be aware of) would unmask a patient's treatment allocation. However, we attempted to reduce bias by using a detailed transfusion protocol. The protocol was strictly followed, as indicated by almost identical hemoglobin concentrations for both groups throughout the study period. Strict adherence to the transfusion protocol was also observed for the administration of hemostatic blood components (allogeneic FFP, platelets), as reported in Results.

In conclusion, the prophylactic administration of a therapeutic dose (15 ml/kg) of autologous FFP after CPB failed to reduce blood loss and transfusion requirements in patients undergoing uncomplicated, elective, primary coronary artery bypass surgery. Prophylactic administration contributes to the inappropriate use of FFP in coronary artery bypass surgery, exposes patients to unnecessary risks, places unnecessary demands on the blood resource, and produces unnecessary costs.

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