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CRITICAL CARE

Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study

N. Rahe-Meyer[1]*, M. Pichlmaier[2], A. Haverich[2], C. Solomon[1], M. Winterhalter[1], S. Piepenbrock[1] and K. A. Tanaka[3]

[1]*Department of Anaesthesiology and* [2]*Department of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany.* [3]*Department of Anesthesiology, Emory University, School of Medicine, Atlanta, GA, USA*

*Corresponding author. E-mail: rahe-meyer.niels@mh-hannover.de

Background. Bleeding diathesis after aortic valve operation and ascending aorta replacement (AV–AA) is managed with fresh-frozen plasma (FFP) and platelet concentrates. The aim was to compare haemostatic effects of conventional transfusion management and FIBTEM (thrombo-elastometry test)-guided fibrinogen concentrate administration.

Methods. A blood products transfusion algorithm was developed using retrospective data from 42 elective patients (Group A). Two units of platelet concentrate were transfused after cardiopulmonary bypass, followed by 4 u of FFP if bleeding persisted, if platelet count was $\leq 100 \times 10^3 \ \mu l^{-1}$ when removing the aortic clamp, and *vice versa* if platelet count was $> 100 \times 10^3 \ \mu l^{-1}$. The trigger for each therapy step was ≥ 60 g blood absorbed from the mediastinal wound area by dry swabs in 5 min. Assignment to two prospective groups was neither randomized nor blinded; Group B (*n*=5) was treated according to the algorithm, Group C (*n*=10) received fibrinogen concentrate (Haemocomplettan® P/Riastap, CSL Behring, Marburg, Germany) before the algorithm-based therapy.

Results. A mean of 5.7 (0.7) g fibrinogen concentrate decreased blood loss to below the transfusion trigger level in all Group C patients. Group C had reduced transfusion [mean 0.7 (range 0–4) u *vs* 8.5 (5.3) in Group A and 8.2 (2.3) in Group B] and reduced postoperative bleeding [366 (199) ml *vs* 793 (560) in Group A and 716 (219) in Group B].

Conclusions. In this pilot study, FIBTEM-guided fibrinogen concentrate administration was associated with reduced transfusion requirements and 24 h postoperative bleeding in patients undergoing AV–AA.

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Complex cardiac surgery is frequently accompanied by excessive perioperative bleeding because of coagulation system impairment, inadequate surgical haemostasis, or both.[1] Bleeding increases the risk of re-exploration, allogeneic blood transfusion, or perioperative myocardial infarction, and consequently, associated morbidity and mortality.[2] Aortic valve operation and ascending aorta replacement (AV–AA) typically involves hypothermia, prolonged cardiopulmonary bypass (CPB), and large graft anastomoses, and is associated with an increased risk of

intra- and postoperative blood loss and high transfusion rates.[3] [4] Conventional haemostatic therapy consists of transfusion of allogeneic blood products that include fresh-frozen plasma (FFP), platelet concentrate, and cryoprecipitate. However, although the use of these products was developed empirically, their haemostatic efficacy has not been evaluated thoroughly in the surgical setting.[5] [6]

Haemocomplettan® P (brand name in Europe)/Riastap (brand name in USA) (CSL Behring, Marburg, Germany) is a highly purified, lyophilized, virus-inactivated

fibrinogen concentrate obtained from human plasma that can be rapidly reconstituted without the need for thawing and cross-matching, which are necessary for FFP and cryoprecipitate. The administration of fibrinogen concentrate was originally reserved for replacement therapy in congenital fibrinogen deficiency, and in the USA, Riastap is only approved for this indication. In the meantime, European reports on haemostatic therapy with Haemocomplettan® P in acquired perioperative deficiency of fibrinogen have been published.[7–11] Acquired fibrinogen deficiency occurring during and after CPB is associated with increased bleeding after cardiac surgery.[12 13] However, the haemostatic efficacy of fibrinogen concentrate in correcting such deficiency in complex cardiac surgery has not been investigated to date.

To reduce blood component transfusion in cardiac surgery, point-of-care methods such as thrombelastography/thromboelastometry have been applied in algorithms supporting bleeding management in relation to blood clotting quality.[14–16] Thromboelastometry (ROTEM®; Pentapharm GmbH, Munich, Germany) assesses the viscoelasticity of whole blood. One of the ROTEM® tests, the FIBTEM test, provides prompt information on the clot strength specifically attributed to fibrin/fibrinogen using cytochalasin-D-induced inactivation of platelets *in vitro*.[17] This test may be used to guide the administration of fibrinogen concentrate for prompt haemostatic therapy.[9–11]

We hypothesized that postoperative haemostasis could be improved by increasing plasma fibrinogen concentrations, since bleeding complications were observed to be lower in patients with high perioperative fibrinogen concentrations.[12 13] The primary aim of this pilot study was to evaluate whether FIBTEM-guided intraoperative fibrinogen repletion was able to reduce the use of allogeneic blood products and postoperative bleeding in patients undergoing AV–AA.

Methods

The study protocol was approved by the institutional review board of the Hannover Medical School, and informed written consent was obtained from patients enrolled in the prospective part of the study. The inclusion criterion was elective AV–AA throughout the study. Exclusion criteria for both the retrospective and the prospective parts of the study were: any known congenital or acquired bleeding disorders, severe liver disease or heparin-induced anticoagulation effects, despite protamine therapy, age under 18 yr, pregnancy or nursing, redo surgery, emergency operation, and positive anamnesis for intake of platelet aggregation inhibitors within 5 days of surgery.
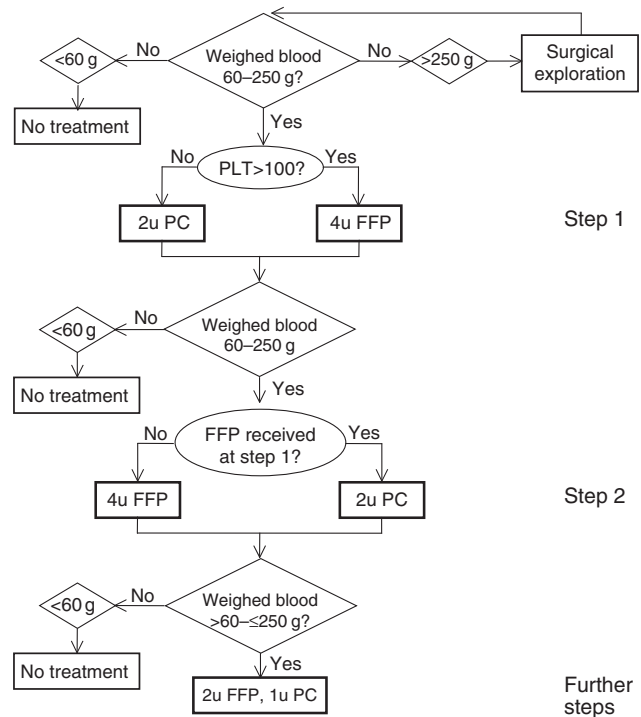
Transfusion algorithm

Retrospective data from all 42 patients undergoing elective AV–AA in 2006 selected according to the inclusion and exclusion criteria were obtained from medical records (Group A). Patients had been transfused without a standardized transfusion protocol or point-of-care laboratory testing, and had received on average 4 u of FFP and 2 u of platelet concentrate during and the first 24 h after the operation. On the basis of these data and on algorithms described in the literature,[14 15] a two-step blood products transfusion algorithm for patients undergoing AV–AA was developed (Fig. 1).

In addition, we developed a method for quantifying mediastinal bleeding after the completion of heparin neutralization and surgical haemostasis after weaning from CPB. The method was also applied after each therapy step. The surgical field was thoroughly covered with sterile, dry surgical swabs of known weight after all blood had been removed using a suction device. Surgical swabs were carefully removed after 5 min and blood loss was determined by weighing the swabs and measuring the weight increase.[18]

On the basis of preliminary measurements, the cut-off value chosen for clinically relevant diffuse, microvascular bleeding was 60 g. If between 60 and 250 g had been absorbed (i.e. $720–3000 \text{ g of blood h}^{-1}$), two-step transfusion therapy was initiated (Fig. 1). Patients with blood loss >250 g were surgically re-explored and blood loss re-evaluated in the same way. The first step of haemostatic therapy was administered based on the platelet count. If the platelet count measured at the removal of the aortic clamp was $>100 \times 10^3 \text{ }\mu\text{l}^{-1}$, patients were initially transfused with 4 u of FFP; if it was $\leq 100 \times 10^3 \text{ }\mu\text{l}^{-1}$, therapy

Fig 1 Flow chart of transfusion algorithm. FFP, fresh-frozen plasma; PC, platelet concentrates; PLT, platelet count ($\times 10^3 \text{ }\mu\text{l}^{-1}$); u, unit.

was initiated with a transfusion of 2 u of platelet concentrate. Each transfusion was to be completed in 15 min and followed by blood loss measurement. If blood loss was not reduced to <60 g, patients who received FFP in the first therapy step then received 2 u of platelet concentrate, and those who initially received platelet concentrate were given 4 u of FFP (Fig. 1). If diffuse, microvascular bleeding persisted, patients received a further 2 u of FFP and 1 u of platelet concentrate consecutively. After successful haemostatic therapy, defined as a 5 min blood loss <60 g in subsequent assessments, the thorax was closed.

Prospective treatment groups

Fifteen patients undergoing AV–AA were prospectively enrolled into Groups B and C. Five consecutive patients in Group B received transfusion according to the pre-defined blood products transfusion algorithm. Patients in Group C received fibrinogen concentrate before being transfused according to the transfusion algorithm. Fibrinogen concentrate dose was determined based on maximum clot firmness (MCF) in the FIBTEM test performed at the removal of the aortic clamp. With the goal of increasing FIBTEM MCF in Group C to ∼22 mm, the following formula was established:

$$\text{Fibrinogen concentrate}\,(g) =$$
$$[22\,(mm) - \text{FIBTEM MCF}\,(mm)] \times \text{body weight}\,(kg) \times c$$
$$c = \frac{0.5\,(g)}{1\,(mm) \times 70\,(kg)}$$

Therefore, the dose of fibrinogen concentrate equalled (22–FIBTEM MCF)×body weight/140. According to this formula, a patient of 70 kg requires a fibrinogen concentrate dose of ∼0.5 g to elevate FIBTEM MCF by ∼1 mm.

The dose was rounded to a whole number of grams; the maximum fibrinogen concentrate dose was arbitrarily set at 6 g. After fibrinogen administration, patients in Group C received transfusion according to the algorithm applied to Group B, if bleeding persisted (Fig. 1).

For both Groups B and C, the transfusion of red blood cells (RBC) was administered to maintain haematocrit values between 23% and 25% on CPB, reaching 28% after CPB when the blood from the extracorporeal circulation system was re-infused into the patient.

The primary endpoint of the study was transfusion of allogeneic blood products after CPB in the 24 h postoperative period; the secondary endpoint was the 24 h postoperative blood loss. Postoperative complications were documented until the patient was discharged.

Intraoperative management

All patients underwent general anaesthesia induced with etomidate, fentanyl, and cisatracurium. For maintenance of anaesthesia, sevoflurane was titrated to an end-tidal concentration of 1–2% until aortic cross-clamping on CPB. For the duration of CPB, propofol was infused and additional boluses of fentanyl were given every 30 min during the operation. All patients received 500 ml of Ringer's lactate solution and 500 ml of gelatine polysuccinate (Gelafundin® 0.026, Serumwerk, Bernburg, Germany) at the start of anaesthesia.

After aortic cannulation and administration of heparin 400 IU kg^{-1} (Heparin-Natrium-25000-ratiopharm®, Merckle GmbH, Blaubeuren, Germany), an extracorporeal circulation system was established, and the ascending aorta was replaced with an artificial graft (Hemashield Gold™ or Platin™, Woven Double Velour Vascular Graft, Boston Scientific International SA, Boston, MA, USA). Moderate hypothermia of 32°C was used routinely in all patients. Before CPB, 1 million kallikrein-inhibiting units (KIU) of aprotinin were administered, with an additional 1 million KIU in the CPB priming solution. After the initial anticoagulation, additional doses of heparin were given to maintain activated clotting time over 480 s. The system was primed with 1000 ml of Ringer's lactate solution, 500 ml of sodium chloride, and 40 ml of 8.4% sodium bicarbonate. After aorta replacement, patients were re-warmed to a bladder temperature of 36.5°C and weaned from CPB. Heparin was neutralized with protamine sulphate (Protamin Valeant, Valeant Pharmaceuticals GmbH, Eschborn, Germany) immediately after CPB. After surgery, patients were transferred to the intensive care unit (ICU).

Haematological evaluations

Blood samples were drawn serially from the radial artery catheter (20 gauge) into commercially available pre-filled collection vials (Sarstedt, Nuembrecht, Germany), which contained heparin, citrate, or ethylenediamine tetracetic acid as the anticoagulant. Blood was sampled before operation (before induction of anaesthesia), at removal of the aortic clamp, at the end of CPB, after intraoperative haemostatic therapy, and 24 h after the operation.

Activated partial thromboplastin time (aPTT; Kaolin, Stago Diagnostica, Asnières, France), prothrombin time (PT; Neoplastine®, Stago Diagnostica), and fibrinogen concentration (Clauss method: optical read-out) were determined using the STA-R® Analyzer (Stago Diagnostica & Roche, Germany). Platelet count and haematocrit were measured using the Sysmex XE-2100 (Roche Diagnostics, Mannheim, Germany). Platelet counts were available within 10–15 min of testing.

A four-channel ROTEM® device (Pentapharm, Munich, Germany) was used to perform thromboelastometric analyses of whole blood samples as described previously.[9 10 16 17] ROTEM® analyses were performed using 300 μl of whole blood and 20 μl of 0.2 M calcium chloride together with specific activators. In the EXTEM test, the activator used

was rabbit brain thromboplastin. In the FIBTEM test, cytochalasin-D was added to rabbit brain thromboplastin in order to inhibit the contribution of platelets to the formation of the fibrin clot. The following parameters were recorded for the ROTEM® tests: clotting time [CT (s); time from the start of the test until a clot firmness of 2 mm is detected] and MCF (mm).

Blood count, coagulation factors, and thromboelastometry were measured at the start of the procedure, after CPB, after coagulation therapy, and 24 h after operation. Only platelet count and thromboelastometry at the time point of unclamping the aorta were relevant for the planning of the coagulation therapy, so no other measures were recorded at this stage. ROTEM® results were concealed from the attending anaesthetists, surgeons, and intensive care physicians. The measurements were performed by a member of the anaesthesiology department not involved in patient operation management.

Statistical analysis

The differences between the groups were analysed with regard to patient characteristics, intraoperative and 24 h postoperative transfusion of allogeneic blood products, and 24 h postoperative blood loss. The primary endpoint, the use of allogeneic blood products, was compared between the retrospective Group A and the prospective fibrinogen therapy Group C. The secondary endpoint, the 24 h postoperative blood loss, was compared between the same two groups. Group B was used to assess whether significant differences in transfusion parameters would be induced by standardizing the transfusion practice compared with the retrospective Group A. Because detailed coagulation analyses were not available in Group A (historical control) during CPB and at the end of CPB, data obtained from the prospective conventional therapy (Group B) were compared with those from Group C. On the basis of our previous experience with ROTEM® assays, a minimal sample size of 5 was needed to detect a 30% change in MCF values with a β-value of >0.8 and an α-value of <0.05. Data are presented as mean (SD). Continuous variables were analysed with a Mann–Whitney U-test; categorical variables were analysed using the χ^2 test. A P-value of ≤ 0.05 was considered to be statistically significant.

Results

All patient groups were similar with regard to preoperative characteristics (Table 1). For the prospective groups (B and C), the main parameters guiding the initial treatment step were comparable, namely platelet count at removal of the aortic cross-clamping (mean 135×10^3 and 137×10^3 μl^{-1}, respectively) and the 5 min blood loss assessment after weaning from CPB [mean 137 (54) and 133 (55) g, respectively].

Five patients were recruited to the prospective, blood products therapy group (B). Mean 5 min blood loss was 84 (12) g after the first therapy step. As a result of a defective FFP bag, one patient only received 3 u of FFP. One patient had blood loss below 60 g, and therefore no additional haemostatic therapy was required. Intraoperative bleeding was successfully managed after the second therapy step in all patients; the mean 5 min blood loss decreased to 49 (6) g. The retrospective and the prospective group treated with allogeneic blood products, Groups A and B, were comparable regarding bleeding and transfusion parameters, that is, these were not influenced by the introduction of the standardized transfusion algorithm. The patients in these groups were also comparable with regard to postoperative parameters in the ICU. Regarding standard laboratory data, preoperative levels of haematocrit appeared lower in Group B than in Group A, but the difference was not significant (Table 2). Other laboratory parameters, including platelet count, were comparable at all times.

The amount of RBC concentrate used on CPB was comparable between the groups (Table 3). The 10 patients recruited to the prospective Group C received a mean dose of 5.7 (0.7) g fibrinogen concentrate. This effectively reduced the 5 min blood loss from 133 (55) g after weaning from CPB to 32 (18) g (<60 g in all patients). Therefore, according to the transfusion algorithm, no additional intraoperative administration of FFP or platelet concentrates was necessary after the end of CPB in this group. After the operation and during the first 24 h in the ICU, only two patients treated with fibrinogen concentrate required transfusion [mean 0.7 (range 0–4) u in Group C *vs* 8.5 (5.3) and 8.2 (2.3) u in Groups A and B, respectively] (Table 3). Group C had lower 24 h drainage than the retrospective Group A (Table 3). Intubation time and

Table 1 Characteristics in patients undergoing AV–AA. Data presented as mean (range), mean (SD) or absolute

	Group A (retrospective) (*n*=42)	Group B (*n*=5)	Group C (+fibrinogen) (*n*=10)
Age (yr)	57 (33–89)	61 (47–76)	57 (25–76)
Weight (kg)	84 (14)	94 (8)	90 (20)
Body mass index (kg m^{-2})	27 (5)	27 (2)	29 (5)
Female (*n*)	14	0	2
Coronary heart disease (*n*)	6	1	1
Peripheral vascular disease (*n*)	3	0	2
Cerebrovascular disease (*n*)	2	0	0

Table 2 Laboratory parameters in patients undergoing AV–AA. Data presented as mean (SD). aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; PT, prothrombin time. *P<0.05 Group C *vs* Group A; †P<0.05 Group C *vs* Group B (P<0.05); there were no statistically significant differences between Groups A and B

Laboratory data	Group A (n=42)	Group B (n=5)	Group C (+fibrinogen) (n=10)
Preoperative laboratory parameters			
Haematocrit (%) (normal range: 41.5–50.4)	40 (5)	35 (6)	39 (5)
PT (s) (normal range: 11–13.5)	15 (3)	14 (1)	14 (1)
aPTT (s) (normal range: 26–35)	32 (8)	29 (2)	29 (3)
Platelet count (10^3 μl^{-1}) (normal range: 150–450)	202 (63)	204 (46)	196 (33)
Fibrinogen (g litre^{-1}) (normal range: 2.0–4.5)	3.4 (0.6)	3.2 (1.0)	3.3 (1.0)
Removal of aortic clamp			
Platelet count (10^3 μl^{-1})		135 (43)	137 (38)
End of CPB			
Haematocrit (%)		29 (2)	29 (4)
PT (s)		19 (1)	20 (2)
aPTT (s)		31 (3)	32 (2)
Platelet count (10^3 μl^{-1})		103 (26)	104 (23)
Fibrinogen (g litre^{-1})		2.1 (0.6)	2.2 (0.6)
After coagulation therapy			
Haematocrit (%)	28 (3)	25 (3)	28 (4)†
PT (s)	17 (1)	18 (1)	18 (1)
aPTT (s)	33 (5)	32 (3)	32 (2)
Platelet count (10^3 μl^{-1})	128 (40)	142 (24)	115 (31)
Fibrinogen (g litre^{-1})	2.2 (0.4)	2.1 (0.3)	3.6 (0.6)*,†
First postoperative day			
Haematocrit (%)	31 (3)	31 (4)	31 (5)
PT (s)	17 (2)	16 (1)	16 (1)
aPTT (s)	40 (16)	36 (5)	36 (7)
Platelet count (10^3 μl^{-1})	135 (31)	129 (41)	132 (33)
Fibrinogen (g litre^{-1})	4.4 (0.6)	4.3 (0.9)	4.4 (0.7)

Table 3 Intra- and postoperative parameters in patients undergoing AV–AA. Data presented as mean (SD) or absolute. CPB, cardiopulmonary bypass; ICU, intensive care unit; prolonged ventilatory support, ventilatory support >40 h. *P<0.05 Group C *vs* Group A; †P<0.05 Group C *vs* Group B

Parameters	Group A (n=42)	Group B (n=5)	Group C (+fibrinogen) (n=10)
Intraoperative			
Aortic clamp time (min)	72 (21)	72 (19)	68 (31)
CPB time (min)	107 (25)	108 (29)	100 (40)
Lowest temperature on CPB (°C)	31.3 (2.2)	31.6 (2.5)	32.8 (2.5)
Red blood cells on CPB (u)	1.1 (1.8)	0.8 (1.3)	0.7 (1.1)
5 min blood loss (ml) after			
weaning from CPB	N/A	137 (54)	133 (55)
fibrinogen concentrate	N/A	N/A	32 (18)
first therapy step	N/A	84 (12)	N/A
second therapy step	N/A	49 (6)	N/A
Postoperative			
Patients who did not receive any allogeneic blood after CPB and on first day ICU (n)	1	0	8*,†
ICU time to extubation (h)	13 (12)	12 (5)	9 (5)
ICU time (h)	36 (26)	31 (21)	20 (5)*,†
Re-exploration for bleeding (n)	2	1	0
Postoperative atrial fibrillation (n)	6	1	1
Prolonged ventilatory support (n)	1	0	0
Major neurological events (n)	0	0	0
30 day mortality (n)	0	0	0
Postoperative hospitalization (days)	10 (3)	12 (12)	10 (2)
Units transfused/volume drained after CPB and during the first 24 h in ICU			
Red blood cells (u)	2.4 (2.5)	2.4 (1.1)	0.5 (1.1)*,†
Fresh-frozen plasma (u)	4.5 (2.1)	4.2 (1.1)	0.2 (0.6)*,†
Platelet concentrate (u)	1.6 (1.7)	1.6 (0.9)	0.0 (0.0)*,†
Total blood cell concentrates (u)	8.5 (5.3)	8.2 (2.3)	0.7 (1.5)*,†
Drainage volume (ml)	793 (560)	716 (219)	366 (199)*,†

ICU stay duration were shorter and complication rates lower in Group C (Table 3).

Standard laboratory analyses showed that preoperative values were comparable across the groups (Table 1). For all groups, the coagulation parameters were similarly affected during CPB, reflected by the analysis performed upon removal of the aortic clamp (Tables 2 and 4). Analysis performed after weaning from bypass showed no

Table 4 ROTEM® values in patients undergoing AV–AA. Data presented as mean (SD). CPB, cardiopulmonary bypass; EXTEM®, ROTEM® test with extrinsic activation of coagulation; FibTEM®, ROTEM® test with extrinsic activation of coagulation and platelet inhibition with cytochalasin D; CT, clotting time; MCF, maximal clot firmness. *P<0.05 Group C *vs* Group B

ROTEM® values	Group B (n=5)	Group C (+fibrinogen) (n=10)
Preoperative		
EXTEM® CT (s) (normal range: 35–80)	71 (7)	69 (7)
EXTEM® MCF (mm) (normal range: 53–72)	64 (5)	62 (5)
FibTEM® MCF (mm) (normal range: 9–25)	15 (3)	14 (4)
Removal of the aortic clamp		
EXTEM® CT (s)	104 (32)	132 (73)
EXTEM® MCF (mm)	58 (6)	56 (6)
FibTEM® MCF (mm)	12 (2)	11 (3)
End of CPB		
EXTEM® CT (s)	87 (10)	92 (14)
EXTEM® MCF (mm)	57 (4)	55 (5)
FibTEM® MCF (mm)	12 (2)	11 (3)
After coagulation therapy		
EXTEM® CT (s)	76 (4)	69 (10)
FibTEM® MCF (mm)	12 (2)	20 (3)*
First postoperative day		
EXTEM® CT (s)	7 (9)	73 (11)
EXTEM® MCF (mm)	64 (4)	63 (5)
FibTEM® MCF (mm)	22 (6)	21 (3)

significant differences between the groups. After the final therapy step, laboratory values showed a higher plasma concentration of fibrinogen in Group C than in Groups A and B. However, after 24 h, the fibrinogen plasma concentration was uniformly high in all the groups.

Preoperative ROTEM® data were comparable between Groups B and C (Table 4). After therapy, Groups B and C had similar EXTEM values, but Group C had higher FIBTEM values (Table 4). However, after 24 h, FIBTEM and EXTEM values were comparable and within the normal range in both groups.

Discussion

In this pilot study, haemostatic therapy with fibrinogen concentrate targeting a high plasma fibrinogen level in AV–AA patients resulted in a reduction in transfusion of allogeneic blood products and drainage volume compared with a historical control group that received conventional haemostatic therapy.

Before haemostatic therapy, at the end of CPB, coagulation disturbances seen in laboratory tests were comparable between the conventional therapy groups (A and B) and prospective fibrinogen therapy group (Group C). Both groups had prolonged PT, decreased platelet counts, and decreased fibrinogen levels compared with baseline. The administered fibrinogen concentrate [5.7 (0.7) g, representing ~285 ml] restored fibrinogen plasma to baseline levels without affecting PT and platelet count. Despite the lower transfusion of RBC, FFP, and platelet concentrate in Group C, the laboratory data on haematocrit, platelet count, PT/aPTT, and fibrinogen were comparable among the three groups at 24 h after surgery.

There are currently ongoing discussions in the literature concerning the critical level of plasma fibrinogen in relation to perioperative bleeding.[12][13][19][20] There are experimental and clinical data describing a protective effect of high plasma fibrinogen levels. A study by Velik-Salchner and colleagues[21] reported that the use of fibrinogen concentrate (250 mg kg^{-1}) was more effective than platelet concentrate in a porcine hepatic laceration model in the presence of thrombocytopenia (platelet count $<30\times10^3$ mm^{-3}). There are ~40 000–80 000 glycoprotein IIb/IIIa receptors on a single, activated platelet, and the number of these receptors is relatively constant after CPB.[22] Thrombin generation is decreased after CPB,[23] but one molecule of thrombin can cleave up to 1680 molecules of fibrinogen.[24] Assuming a simple enzyme–substrate reaction (Michaelis–Menten equation) between thrombin and fibrinogen, the Michaelis constant (K_m) value of fibrinogen at 2 g litre^{-1} (6 µM) represents half of the maximal reaction rate between thrombin and fibrinogen.[25] According to the Michaelis–Menten equation, the targeted fibrinogen level of 3.6 g litre^{-1} (or 10.7 µM) would nearly maximize the interaction between fibrinogen and the amount of thrombin available after CPB, resulting in improved haemostasis. The threshold level of fibrinogen was also evaluated in obstetric patients who developed severe post-partum haemorrhage, in which a fibrinogen level $\leq$2 g litre^{-1} had 100% positive predictive value for bleeding and a level $>$4 g litre^{-1} had 79% negative predictive value for bleeding.[19] Other clinical studies have shown that a low fibrinogen concentration better predicts increased bleeding after prolonged CPB.[12][13] In another clinical setting, Heindl and colleagues[11] previously described the use of fibrinogen (7–8 g) in patients with major traumatic bleeding refractory to standard coagulation therapy. Since this first report, fibrinogen concentrate has been shown to improve haemostasis in acquired hypofibrinogenaemia associated with cardiac surgery, liver transplantation, trauma, placental abruption, dilutional coagulopathy during complex orthopaedic procedures, and in disseminated intravascular coagulation as a result of massive blood loss and transfusion.[7–10]

Using fibrinogen concentrate as a first-line therapy to correct postoperative bleeding and to reduce the use of FFP, platelet concentrate, or both seems to be a reasonable approach as these allogeneic blood products are associated with various adverse outcomes.[26][27] In addition, as the average concentrate of fibrinogen in FFP is 2.5 g litre^{-1}, FFP cannot be used for haemostatic therapy targeting a plasma fibrinogen level higher than this.

Fibrinogen concentrate administration was guided by FIBTEM (clot strength in the presence of platelet inhibition) using the empirical target MCF of 22 mm with an arbitrary limit for the maximal dose set at 6 g fibrinogen concentrate. This strategy resulted in a mean plasma

fibrinogen concentration increase (from 2.2 to 3.6 g litre^{-1}) and an increase in mean FIBTEM MCF from 11 to 20 mm. The decision whether to administer fibrinogen concentrate had to be made within 10 min after CPB when diffuse bleeding was diagnosed. The FIBTEM test is rapid and requires no centrifugation of the sample, a time-consuming step otherwise necessary in the standard laboratory-based assessment of fibrinogen concentration. In contrast to the optical read-out of the Clauss method, which measures the time to change in turbidity caused by fibrin formation and estimates fibrinogen plasma concentration from a calibration curve, the FIBTEM provides information on the mechanical strength of the clot. For all these reasons, we considered the FIBTEM (ROTEM®) to be the optimal bedside assay to guide the dosage of fibrinogen concentrate in this setting.

Because fibrinogen is an acute-phase protein, its level increases gradually after surgical procedures.[13] Even though Group C received a mean of 5.7 g of fibrinogen as haemostatic therapy after weaning from CPB, similar plasma fibrinogen levels in the three groups and similar ROTEM® MCF values in Groups B and C were noted on postoperative day 1 (Tables 2 and 4). This finding may be relevant to the assessment of the safety of administration of fibrinogen concentrate in this setting. In addition, no immediate neurological and cardiorespiratory complications were observed in either group (Table 3).

Other therapeutic options for diffuse bleeding after weaning from CPB may be considered. In countries where fibrinogen concentrate is not available, cryoprecipitate may be used, as it contains a higher concentration of fibrinogen than FFP.[28] Unlike the fibrinogen concentrate we used (Haemocomplettan® P/Riastap, which is pasteurized for 20 h), viral inactivation is not generally applied to cryoprecipitate. Therapy with cryoprecipitate therefore carries a risk of viral transmission equivalent to that of FFP administration.[29] Recombinant activated factor VII (rFVIIa) has been increasingly considered an 'off-label' rescue haemostatic agent in cardiac surgery.[30] Although thrombin generation is decreased after CPB,[23] the balance between thrombin inhibitors such as antithrombin (also decreased after prolonged CPB)[23] and thrombin could be disturbed by adding a drug that generates a 'thrombin burst'. A review of the US Food and Drug Administration's Adverse Event Reporting System found a total of 431 adverse event reports for rFVIIa from 1999 to 2004, including 185 thromboembolic events, 90% of which related to off-label use in patients without haemophilia.[31]

This preliminary study has limitations. First, it was not randomized or blinded and was underpowered to confirm the efficacy and safety of fibrinogen replenishment in complex cardiac surgery. The present data were obtained in a specific population (AV–AA surgery); therefore, our findings may not be appropriate for the management of every type of post-cardiac surgical bleeding diathesis. Secondly, the major endpoints in this study only included the amount of allogeneic blood product use and the 24 h postoperative blood loss. A longer follow-up of large numbers of patients would be necessary to confirm the efficacy of fibrinogen concentrate for haemostatic therapy and to assess safety parameters such as neurological, cardiorespiratory, and infectious complications.

In summary, the present data indicate that fibrinogen concentrate may be effective in reducing both the use of allogeneic blood products and postoperative bleeding in aortic surgical patients. To our knowledge, this was the first time that patients with fibrinogen levels within the normal range (mean 2.2 g litre^{-1}) were substituted with fibrinogen concentrate to achieve an upper normal range (mean 3.6 g litre^{-1}). Compared with the allogeneic blood products, such as FFP, cryoprecipitate, and platelet concentrate, fibrinogen concentrate can be potentially time-saving by precluding the need for cross-matching, thawing, or both. The FIBTEM MCF was an appropriate parameter for dosing fibrinogen concentrate in this setting. A validation study with a prospective, randomized, placebo-controlled design is currently underway.

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