# Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery

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**Objective:** Thoracoabdominal aortic aneurysm operations are associated with extensive blood loss and high requirements for allogeneic blood product transfusion. We assessed the efficacy of intraoperative post–cardiopulmonary bypass administration of fibrinogen concentrate in elective thoracoabdominal aortic aneurysm surgery.

**Methods:** In a retrospective group (group A, n = 12) of patients undergoing elective thoracoabdominal aortic aneurysm surgery, clinically relevant diffuse bleeding after weaning from cardiopulmonary bypass was treated with allogeneic blood products (platelet concentrates, followed by fresh frozen plasma) according to a predetermined algorithm.
In a prospective group (group F, n = 6) a first therapy step with fibrinogen concentrate was added to the algorithm. The dose of fibrinogen concentrate was estimated by using thromboelastometric data (ROTEM FIBTEM). Before each step of hemostatic therapy, blood loss in the range of 60 to 250 g per 5 minutes was confirmed.

**Results:** In group F, administration of 7.8 ± 2.7 g of fibrinogen concentrate established hemostasis, completely avoiding intraoperative transfusion of fresh frozen plasma and platelet concentrates. Transfusion of blood products after cardiopulmonary bypass and during the 24 hours after surgical intervention was markedly lower in group F than in group A (2.5 vs 16.4 units; 4/6 patients in group F required no transfusion of blood products), as was 24-hour drainage volume (449 vs 1092 mL). Fibrinogen plasma levels, standard coagulation parameters, and hemoglobin and hematocrit values were comparable between the 2 groups on the first postoperative day.

**Conclusions:** FIBTEM-guided post–cardiopulmonary bypass administration of fibrinogen concentrate resulted in improved intraoperative management of coagulopathic bleeding in thoracoabdominal aortic aneurysm operations and reduced transfusion and 24-hour drainage volume.

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Thoracoabdominal aortic aneurysm (TAAA) operations are frequently complicated by excessive perioperative bleeding, most commonly caused by impairment of the coagulation system.[1] Patients with aortointimal disease are in a hyperfibrinolytic state because of abnormal endothelial expression of tissue plasminogen activator, which correlates with the chronic consumption coagulopathy accompanying aortic aneurysm.[2] Extracorporeal circulation (ECC) exerts an additional deleterious effect on hemostasis through activation of coagulation and fibrinolysis, consumption coagulopathy, and decreased platelet function.[3,4] Excessive bleeding enhances the risk of rethoracotomy, transfusion, or perioperative myocardial infarction, leading to increased morbidity and mortality.[5] Although TAAA surgery has improved over recent years, the perioperative consumption of allogeneic blood products and the risk of bleeding remain high.[6]

The standard hemostatic treatment is transfusion of nonerythrocyte allogeneic blood products: fresh frozen plasma (FFP), platelet concentrates (PCs), and, in some countries, cryoprecipitate. However, there is an inherent risk of transmission of pathogens with transfusion of allogeneic blood products, which can be associated with serious adverse effects.[7,8] Preemptive transfusion, in which blood products are transfused before laboratory abnormalities are recognized, plays a central role in the intraoperative transfusion strategy for TAAA operations and has shown improved outcome compared with treatment algorithms based on laboratory measurements.[9]

The possibilities for reducing transfusion of allogeneic blood products after cardiac surgery have been investigated recently. Assessment of clot formation and strength, measured by using viscoelastic methods (thromboelastography [TEG] or thromboelastometry [ROTEM]), is useful for the diagnosis of intraoperatively acquired coagulation

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**Abbreviations and Acronyms**

CPB = cardiopulmonary bypass
ECC = extracorporeal circulation
EXTEM = ROTEM test with extrinsic activation of coagulation
FFP = fresh frozen plasma
FIBTEM = ROTEM test with extrinsic activation of coagulation and platelet inhibition with cytochalasin D
ICU = intensive care unit
MCF = maximum clot firmness
PC = platelet concentrate
RBC = red blood cell
ROTEM = thromboelastometry
TAAA = thoracoabdominal aortic aneurysm
TEG = thromboelastography

disturbances and has resulted in the development of coagulation therapy algorithms and consequent reductions in blood transfusion and associated hospitalization costs.[10,11] Administration of coagulation factor concentrates might also support the reduction of perioperative transfusion. Haemocomplettan P (CSL Behring, Marburg, Germany) is a purified, virus-inactivated fibrinogen concentrate obtained from lyophilized plasma. Fibrinogen concentrate was used initially for replacement therapy in inherited fibrinogen deficiencies but might also correct the fibrinogen deficit associated with bleeding after cardiac surgery.[4,12]

This prospective trial assesses the efficacy of intraoperative coagulation therapy with thromboelastometry-guided fibrinogen concentrate by using a strict transfusion algorithm applied in a homogenous group of patients undergoing TAAA surgery.

## MATERIALS AND METHODS

The study protocol was approved by the Institutional Review Board of Hannover Medical School, and written informed consent was obtained from the patients enrolled in the prospective arm of the study.

### Patients

The retrospective group (group A, allogeneic blood products) included all patients who underwent elective TAAA surgery in Hannover Medical School during 2006 with none of the exclusion criteria listed below (n = 12). Our center uses a standard transfusion algorithm for the treatment of intraoperative clinically relevant diffuse bleeding occurring after cardiopulmonary bypass (CPB), consisting of the administration of PCs and FFP.

For the prospective group (group F, fibrinogen), consisting of 6 patients undergoing elective TAAA surgery, the administration of fibrinogen concentrate (Haemocomplettan P, CSL Behring) was added as step 0 to the algorithm of hemostatic therapy (Figure 1).

Exclusion criteria for both groups included positive anamnesis of bleeding, age less than 18 years, pregnancy, myocardial infarction in the past 3 months, reported platelet aggregation inhibitor therapy within 5 days of surgical intervention, emergency status, and reoperation. As end points after ECC and 24-hour intensive care unit (ICU) treatment, use of blood products and 24-hour postoperative drainage volume data were collected in both groups.

### Assessment of Bleeding Mass

After weaning from ECC, neutralization of heparin, and completion of surgical hemostasis, all blood was removed from the wound area with a suction device. The dry wound area was then thoroughly covered with sterile, dry surgical swabs. After a short period of time (not exactly defined in group A), the surgical swabs were removed to estimate the amount and location of bleeding. In group A the level of bleeding was estimated by the surgeons and the anesthetist and was characterized as low, high, or excessive. High-level bleeding was treated according to the transfusion algorithm, and excessive bleeding required surgical re-exploration.

In group F packing of surgical swabs was restricted to exactly 5 minutes to support an accurate measurement of the blood loss. The extent of blood loss was determined by measuring the difference in weight of the swabs before application and after 5 minutes of adsorbing blood. Blood loss of 60 to 250 g was defined as high-level bleeding and thus represented the trigger for coagulation therapy. Patients with blood loss of less than 60 g received no therapy, whereas blood loss of greater than 250 g was considered to be of surgical origin requiring surgical re-exploration. The procedure was repeated after surgical re-exploration and after each step of hemostatic therapy to determine whether further steps were necessary. The cutoff values applied for the diagnosis of clinically relevant microvascular bleeding (60–250 g) were based on our previous experience in TAAA surgery and are not described in the literature.

### Introduction of the Therapy Step With Fibrinogen Concentrate Into the Standard Transfusion Algorithm

Based on the observation that post-ECC platelet counts in patients with TAAA are usually less than 100,000/$\mu$L, group A received PCs as the first line of therapy when clinically relevant bleeding was observed after CPB. This was followed by therapy with FFP if bleeding persisted at a high level. Further transfusion steps consisted of concomitant transfusion of FFP and PCs. The efficacy of the therapy steps was assessed by using dry surgical swabs.

Patients prospectively enrolled in group F and presenting with measured blood loss of 60 to 250 g were treated according to the treatment algorithm described in Figure 1. Before the administration of PCs or FFP, the administration of fibrinogen concentrate (Haemocomplettan P) was introduced (step 0) to obtain a maximum clot firmness (MCF) of 22 mm in the FIBTEM thromboelastometry test. The rationale for choosing this target value within the normal range for FIBTEM MCF was to balance the reduction of fibrinogen caused by the operation. A FIBTEM MCF of 22 mm correlates with a plasma fibrinogen level of 3.6 g/L, which is within normal values for older populations.[13]

This therapeutic step was followed by reevaluation of the 5-minute bleeding mass. If blood loss had remained greater than 60 g, additional transfusion of PCs or FFP would have been administered depending on the platelet count at the last suture time point (Figure 1). If bleeding had persisted after the 3 consecutive therapy steps described above, further steps of therapy would have consisted of 2 units of FFP and 1 unit of PC. Successful therapy was defined as blood loss of less than 60 g after the final therapy step.

The transfusion of red blood cell (RBC) concentrates was adjusted to maintain hematocrit levels of 23% to 25% during CPB, reaching 27% after CPB when the blood from the ECC system was reinfused into the patient, which is in line with the clinic's standard procedure.

### Fibrinogen Concentrate Dosing Based on Specific Point-of-Care Measurements

The dose of fibrinogen concentrate was calculated based on the value of the MCF parameter in the FIBTEM thromboelastometry test performed at the last suture time point by using the following formula:

$$\textit{Fibrinogen concentrate}\ (g) = (22\ [mm] - \textit{FIBTEM MCF}\ [mm]) \times \textit{Body weight}\ (kg) \times c$$
$$(\textit{where}\ C = 0.5\ [g]/(1\ [mm] \times 70\ [kg])$$

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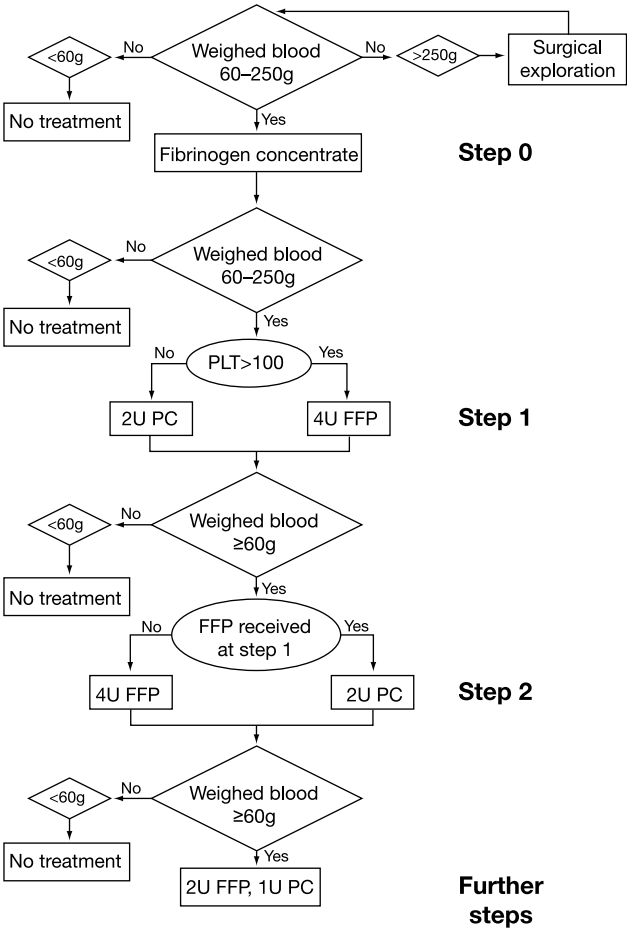


**FIGURE 1.** Flow chart of transfusion algorithm. Platelet count is expressed as 1000/$\mu$L. *PLT*, Platelet count measured at the last suture time point (the suture of the last collateral artery on the aortic graft); *FFP*, fresh frozen plasma; *PC*, platelet concentrates.

The dose of fibrinogen concentrate equaled $(22-FIBTEM\ MCF)\times Body\ weight/140$. According to this formula, a patient of 70 kg requires a fibrinogen concentrate dose of approximately 0.5 g to increase FIBTEM MCF by approximately 1 mm.

The result was rounded to a whole number of grams of fibrinogen concentrate. The upper acceptable limit for MCF in the EXTEM thromboelastometry test was set at 68 mm to minimize the risk of thrombotic complications. Although there is no report of ROTEM values predictive of thrombosis, a value of greater than 68 mm of the maximum amplitude of the clot determined by using TEG was shown to be predictive of thrombotic complications.[14] Because ROTEM MCF values are normally slightly higher than those obtained by using TEG,[15] 68 mm represents a conservative upper limit.

## End Points to Evaluate the Efficacy of Fibrinogen Concentrate

The primary end point for evaluation of the efficacy of fibrinogen concentrate was the transfusion of allogeneic blood products intraoperatively after CPB and during the 24 hours postoperatively. Secondary end points included the number of patients without any transfusion during this timeframe and 24-hour postoperative blood loss (24-hour drainage value).

## Operative and Anesthetic Management

All patients in groups A and F underwent general anesthesia induced with etomidate, 0.3 mg/kg; fentanyl, 8 $\mu$g/kg; and cisatracurium, 0.2 mg/kg. During induction of anesthesia, patients received 500 mL of lactated Ringer's solution and 500 mL of gelatin polysuccinate (Gelafundin 0.026; Serumwerk, Bernburg, Germany), according to the clinic's standard procedures. The trachea was intubated with a double-lumen tracheal tube, and the patients were placed in a right lateral decubitus position. For maintenance of anesthesia, sevoflurane was titrated to an end-tidal concentration of 1% to 2% until institution of ECC. Propofol was infused at 50 to 80 $\mu g\ kg^{-1}\ min^{-1}$, and 4 $\mu$g/kg boluses of fentanyl were administered every 30 minutes for the duration of ECC. A lumbar spinal drain was placed routinely for control of the intraspinal liquid pressure.

All patients underwent the same surgical technique. After administration of pig mucosal heparin (400 IU/kg) and cannulation of the femoral artery and vein, ECC on a standard CPB device (Stöckert SIII; Stöckert Instruments, Munich, Germany) was established, and a proximal anastomosis between the descending aorta and the artificial graft (Hemashield Gold or Platin, Woven Double Velour Vascular Graft; Boston Scientific International SA, Boston, Mass) was performed. Distal anastomosis was completed by means of decannulation of the femoral vein and artery with concomitant protamine sulfate administration. Light hypothermia of 34°C was used in all patients. Both groups received 1 million kallikrein-inhibiting units of aprotinin before ECC and a further 1 million kallikrein-inhibiting units of aprotinin added to the ECC priming solution. After the initial anticoagulation, additional doses of heparin were administered to maintain an activated clotting time of more than 480 seconds (ACT Plus; Medtronic, Minneapolis, Minn). The system was primed with 1000 mL of Ringer's lactate solution, 500 mL of sodium chloride, and 40 mL of sodium bicarbonate (8.4%). At the end of ECC, heparin was neutralized with protamine sulfate, 1 mg of protamine for every 100 U of the total heparin dose; an activated clotting time of less than 150 s indicated reversal of the effects of heparin.

## Hematologic Tests

Serial blood samples were drawn from a radial artery catheter (20 gauge) into Sarstedt collection vials (Sarstedt, Nuembrecht, Germany) containing heparin, citrate, or ethylenediamine tetra-acetic acid as anticoagulant. Blood was sampled at the beginning of the operation (before induction of anesthesia), at the last suture time point (the suture of the last collateral artery on the aortic graft), at the end of ECC, after each therapy step, and 24 hours after the operation.

Activated partial thromboplastin time (APTT Kaolin; STAGO Diagnostica, Asnieres, France), prothrombin time (Neoplastin, STAGO Diagnostica), and fibrinogen concentration (Clauss method: optical read-out) were determined by using the STA-R Analyzer (STAGO Diagnostica). Platelet counts and hematocrit values were measured on the Sysmex XE-2100 (Roche Diagnostics, Mannheim, Germany). Platelet counts were available within 10 to 15 minutes.

A 4-channel ROTEM device (Pentapharm, Munich, Germany) was used for thromboelastometric analyses of the blood samples, as previously described.[10] For each test, the reagents and the blood are pipetted semiautomatically into a single-use plastic cup that is then set onto a plastic pin on a rotating vertical axis guided by ball bearings. The increasing firmness of the clot gradually reduces the movement of the pin. This is continuously detected by using a light source, a reflecting mirror on the rotating axis, and a sensor chip. The reduction in movement is mathematically transformed into clot firmness (amplitude in millimeters) and plotted against time (in seconds), resulting in a thromboelastometric trace. ROTEM tests were performed with 300 $\mu$L of citrated whole blood and 20 $\mu$L of 0.2 mol/L calcium chloride together with specific activators. In the standard global tests to measure clot strength, the activators used were 20 $\mu$L of rabbit brain thromboplastin (ex-TEM reagent) for the EXTEM test and 20 $\mu$L of ellagic acid and rabbit brain partial thromboplastin phospholipid (in-TEM reagent) for the INTEM test. In the FIBTEM test cytochalasin D (fib-TEM reagent)

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was added to the ex-TEM reagent to inhibit the contribution of platelets to the formation of the clot. Clotting time (in seconds; time from the start of the test until the amplitude of 2 mm is detected), clot formation time (in seconds; time for the clot to develop from 2 to 20 mm), MCF (in millimeters), and the alpha angle (the opening angle of the trace) were recorded. Typical EXTEM and FIBTEM thromboelastometric traces are presented in Figure 2.

### Statistical Analysis

The data were analyzed for differences between groups with regard to the preoperative variables, the intraoperative and 24-hour postoperative transfusion of allogeneic blood products, and the 24-hour postoperative blood loss. Data are presented as the mean ± first standard deviation of the individual determinations. Continuous variables were analyzed by using the Mann–Whitney *U* test, and categorical variables were analyzed by using the $\chi^2$ test.

## RESULTS

Groups A and F were comparable with regard to preoperative characteristics (Table 1). There were more female patients in the allogeneic blood products group (group A, 42%) compared with the fibrinogen concentrate group (group F, 12%), but this difference was not statistically significant ($P = .079$). For group F, the main parameters guiding the first step of therapy consisted of platelet count (92,500 ± 37,310/mL) before the suture of the last collateral artery on the vascular graft (FIBTEM MCF was 8.3 ± 4.6 mm at this time point) and the 5-minute blood loss (136.5 ± 86.9 g) after weaning from ECC and after surgical hemostasis. After administration of a mean dose of fibrinogen concentrate of 7.8 ± 2.7 g (range, 5–13 g), the 5-minute blood loss decreased to 42.0 ± 8.9 g, with the result that these patients required only this single therapeutic step. Even though the intraoperative use of RBC concentrates was significantly less in group F (1.3 ± 1 units vs 8.3 ± 3 units in group A), the hematocrit values were comparable in the 2 groups at all times. The total amount of allogeneic blood products transfused intraoperatively after weaning from ECC and in the first 24-hour postoperative period was significantly less in group F (2.5 ± 4.3 units compared with 16.4 ± 4.8 units in group A, Table 2). Four of the 6 patients in group F required no transfusion of allogeneic blood products after weaning from ECC or in the first 24 hours postoperatively, whereas all patients in group A required allogeneic blood product transfusion.

There were differences between the 2 groups in parameters measured during the postoperative period. Patients in group F had significantly lower 24-hour drainage volumes in the ICU (449.2 ± 181.7 mL compared with 1092.5 ± 593.9 mL in group A). Also, intubation time in the ICU and the duration of stay in the ICU were significantly shorter in group F. The total number of hospitalization days was comparable between groups (Table 2). One (20.0%) of the 5 patients in group F and 5 (41.7%) of the 12 patients in group A required prolonged respiratory assistance. No other complications occurred within group F; complications within group A were major neurologic events (2 patients), renal failure (2 patients), and in-hospital death (2 patients). Four patients in

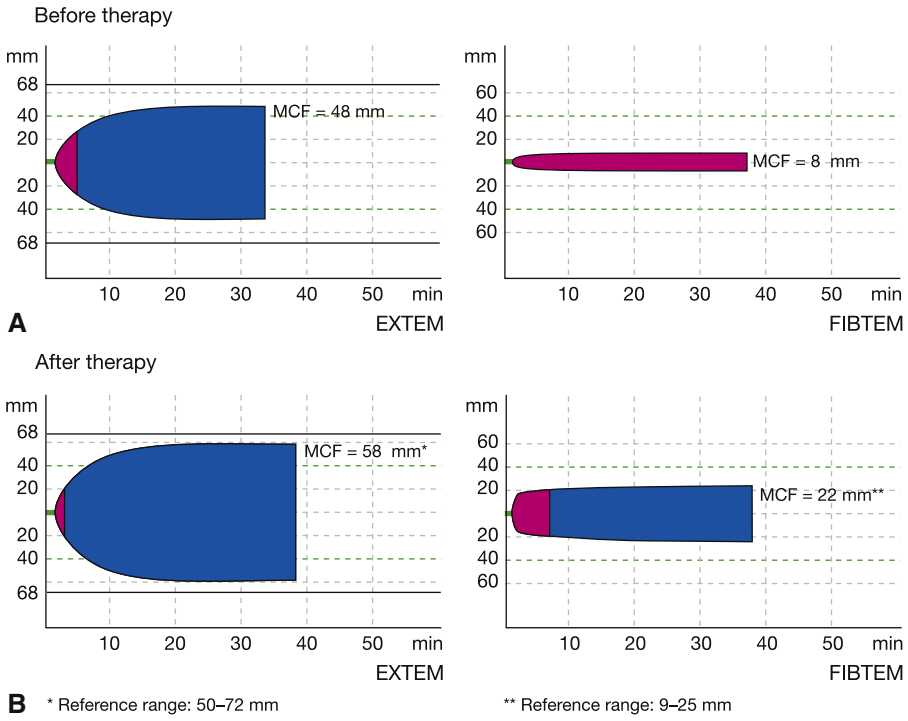


**FIGURE 2.** Examples of thromboelastometry curves (ROTEM). A, Traces before fibrinogen concentrate therapy. The upper MCF limit of 68 mm is indicated by a *solid line*. B, Traces after fibrinogen concentrate therapy. *MCF*, Maximum clot firmness; *EXTEM*, ROTEM test with extrinsic activation of coagulation; *FIBTEM*, ROTEM test with extrinsic activation of coagulation and platelet inhibition with cytochalasin D.

**TABLE 1. Characteristics of patients undergoing thoracoabdominal aortic aneurysm operations**

| Variable | Allogeneic blood products, group A (n = 12) | Fibrinogen concentrate, group F (n = 6) |
|---|---|---|
| Age (y), mean ± SD | 56.9 ± 11.7 | 56.8 ± 8.9 |
| Weight (kg), mean ± SD | 73.2 ± 23.4 | 81.2 ± 18.9 |
| Body mass index (kg/m$^2$), mean ± SD | 23.9 ± 4.2 | 26.6 ± 5.2 |
| Female sex | 5 (42%) | 1 (17%) |
| Chronic pulmonary disease | 5 (42%) | 3 (50%) |
| Neurologic dysfunction | 2 (17%) | 2 (33%) |
| Previous cardiac surgery | 5 (42%) | 2 (33%) |
| Preoperative renal dysfunction | 1 (8%) | 0 (0%) |
| Moderate left ventricular dysfunction | 0 (0%) | 1 (17%) |
| Arterial hypertension | 8 (67%) | 5 (83%) |
| Diabetes (type 1 or 2) | 1 (8%) | 1 (17%) |
| Atrial fibrillation | 2 (17%) | 0 (0%) |
| Coronary heart disease | 2 (17%) | 1 (17%) |
| Peripheral vascular disease | 3 (25%) | 1 (17%) |
| Cerebrovascular disease | 1 (8%) | 0 (0%) |

Preoperative renal dysfunction is defined as a creatinine value of greater than 200 μmol/L preoperatively. Moderate left ventricular dysfunction is defined as a left ventricular ejection fraction of less than 30% to 50%. There were no statistically significant differences between groups. *SD*, Standard deviation.

**TABLE 2. Intraoperative and postoperative parameters in patients undergoing thoracoabdominal aortic aneurysm operations**

| Variable | Allogeneic blood products, group A (n = 12) | Fibrinogen concentrate, group F (n = 6) |
|---|---|---|
| Intraoperative | | |
| Aortic clamp time (min) mean ± SD | 96.7 ± 58.3 | 97 ± 24 |
| CPB time (min) mean ± SD | 139.3 ± 79.2 | 111 ± 35 |
| Deepest temperature on CPB (°C) mean ± SD | 34.1 ± 1.2 | 34.4 ± 0.9 |
| Postoperative | | |
| ICU time to extubation (h), mean ± SD | 42.9 ± 36.3 | 18.5 ± 14.7 |
| ICU time (h), mean ± SD | 115.4 ± 60.2 | 37 ± 18.9* |
| Re-exploration for bleeding | 4 (33%) | 0 (0%) |
| Postoperative atrial fibrillation | 1 (8%) | 0 (0%) |
| Renal failure | 2 (17%) | 0 (0%) |
| Prolonged ventilatory support | 5 (42%) | 1 (17%) |
| Major neurologic events | 2 (17%) | 0 (0%) |
| 30-d Mortality | 2 (17%) | 0 (0%) |
| Postoperative hospitalization (d) | 12.2 ± 5.2 | 14.0 ± 8.4 |
| Patients without any allogeneic blood after CPB | 0 (0%) | 4 (66%)* |
| Units transfused/volume drained after CPB and during the first 24 h in ICU | | |
| Red blood cells (U), mean | 4.1 | 1.0* |
| Fresh frozen plasma (U), mean | 9.1 | 1.0* |
| Platelet concentrate (U), mean | 3.2 | 0.5* |
| Total blood cell concentrates (U), mean | 16.4 | 2.5* |
| Drain volume (mL), mean | 1093 | 449* |

Prolonged ventilatory support is defined as ventilatory support for more than 40 hours. *SD*, Standard deviation; *CPB*, cardiopulmonary bypass; *ICU*, intensive care unit. *Significant difference, group F vs group A: Mann–Whitney *U* test, $P < .05$.

group A required surgical re-exploration; no surgical source of bleeding was identified in any of the 4 patients.

ROTEM results in EXTEM and FIBTEM tests reflected a gradual decrease in clot formation and firmness during the operation (Table 3). After weaning from CPB, clotting time in the INTEM test was 312 ± 108.2 seconds (normal range, 100–240 seconds), clot formation time was 210.5 ± 83.2 seconds (normal range, 30–110 seconds), MCF was 44 ± 7.6 mm (normal range, 50–72 mm), and the alpha angle was 60.2° ± 9.2° (normal range, 70°–83°). After administration of fibrinogen concentrate, the clot formation and firmness parameters improved in both the EXTEM and FIBTEM tests (Table 3 and Figure 2). The 24-hour postoperative (first postoperative day) values were comparable with values obtained after therapy and reflected satisfactory clot formation and firmness (Table 3). At baseline and 24 hours after the operation, the results of standard laboratory analyses were comparable between the 2 groups (Table 4).

## DISCUSSION

In this study the use of fibrinogen concentrate was more effective than FFP and PCs in achieving effective hemostasis and reducing postoperative bleeding and also decreased the use of allogeneic blood products in patients undergoing TAAA operations.

Elective TAAA operations are associated with a high mortality rate of 10.0% to 11.9%.[5] Correction of intraoperative coagulopathy, a cause of major blood loss that often exceeds the patient's intravascular volume,[6] requires massive transfusion of blood products.[9] In a study by Cambria and associates,[16] the requirement for blood products was found to be an independent predictor of perioperative mortality, which directly relates to the need to compensate for acute massive bleeding and, probably to a far lesser extent, to the complications of blood product transfusion. In the quoted study survival rate was significantly correlated with a higher platelet count at admission to the ICU, but the study makes no reference to the changes in fibrinogen plasma concentration.[16] The platelet count below which treatment for bleeding is recommended varies in the literature.[11,17] The requirement for treatment of bleeding is influenced by various factors, including premedication, use and type of ECC, extension of the operation, and center-specific conditions. The same is true for the amount of blood products that should be administered in one therapy step to stop bleeding.[11,17] Transfusions of FFP and PCs are associated with adverse outcomes in cardiac surgery.[8,18] Furthermore, transfusion of FFP can result in a number of volume-related

**TABLE 3. ROTEM values in patients undergoing thoracoabdominal aortic aneurysm operations and treated with fibrinogen concentrate (group F)**

| ROTEM variable | Preoperative | LS time point | End CPB | After fibrinogen concentrate therapy | First postoperative day |
|---|---|---|---|---|---|
| EXTEM | | | | | |
| CT (s; normal range, 38–79 s) | 78.3 ± 10.6 | 88.5 ± 13.5 | 92.3 ± 12.7 | 74.7 ± 11.3 | 75.3 ± 10.8 |
| CFT (s; normal range, 34–159 s) | 82.7 ± 22.1 | 210.2 ± 87.2 | 179.5 ± 79.1 | 81.2 ± 29 | 73.8 ± 19.1 |
| MCF (mm; normal range, 50–72 mm) | 62.8 ± 6.4 | 45.0 ± 11.6 | 48.0 ± 8.5 | 57.5 ± 6.9 | 63.5 ± 4.2 |
| Alpha angle (°; normal range, 63°–83°) | 74.5 ± 3.8 | | 59.5 ± 9.8 | 80.2 ± 2.1 | 77 ± 2.4 |
| FIBTEM | | | | | |
| MCF (mm; normal range, 9–25 mm) | 17.2 ± 5.9 | 7.7 ± 4.3 | 8.3 ± 4.5 | 22.7 ± 5.5 | 24.2 ± 4 |

Values are presented as the mean ± standard deviation. *ROTEM*, Thromboelastometry; *LS*, last suture (the suture of the last collateral artery on the aortic graft); *CPB*, cardiopulmonary bypass; *EXTEM*, ROTEM test with extrinsic activation of coagulation; *CT*, clotting time; *CFT*, clot formation time; *MCF*, maximum clot firmness; *FIBTEM*, ROTEM test with extrinsic activation of coagulation and platelet inhibition with cytochalasin D.

adverse events, such as transfusion-related acute lung injury. However, the number of units of RBCs transfused is the leading predictor of length of hospital stay and complications after CPB surgery.[19] In our study the administration of fibrinogen concentrate as an initial therapy step in group F before following the standard transfusion algorithm was associated with a reduction in the transfusion not only of PCs and FFP but also of RBCs in patients undergoing TAAA surgery. These findings suggest a beneficial effect of fibrinogen concentrate as hemostatic agent in this setting. The introduction of therapy with fibrinogen concentrate did not delay initiating the treatment algorithm because its preparation fitted the timeframe usually required to order and prepare FFP or PCs. Compared with the conventional non–virus-inactivated allogeneic blood products, such as FFP, cryoprecipitate, and PCs, the administration of fibrinogen concentrate might be time-saving by precluding thawing, cross-matching, or both. In our study administration of fibrinogen concentrate was sufficient to stop bleeding in all patients, and the remaining steps in the PC- and FFP-based algorithm were not required.

The gravimetric measurement of blood loss was based on the assumption that 1 mL of blood weighs 1 g, even though the average specific gravity of red corpuscles is 1.0293 and that of plasma is 1.0270.[20] In a study by Johar and colleagues,[21] measurement was performed by using dry surgical swabs that were weighed immediately after contamination with blood to avoid loss through evaporation and to accelerate the therapeutic decision. Careful surgical hemostasis, including packing of the thorax and the abdomen with surgical swabs, is standard practice in TAAA surgery. Thus major sources of bleeding usually do not go undetected. In our study packing was restricted to exactly 5 minutes to accurately calculate the blood loss. Weighing the surgical swabs after 5 minutes of packing might help differentiate between excessive macrovascular and microvascular bleeding, as well as between clinically relevant and nonrelevant or ceased bleeding. A prospective trial that uses a standardized method of assessment of the dryness of the surgical field, such as the 5-minute blood loss method presented in our study, might help clarify this aspect.

Fibrinogen concentrate was chosen for first-line hemostatic therapy based on new research showing that low perioperative fibrinogen concentrations correlate with bleeding.[4,12,22] In a multivariate analysis by Charbit and associates,[23] fibrinogen was the only marker associated with the occurrence of severe postpartum hemorrhage, with a 79% negative predictive value of fibrinogen greater than 4 g/L and a 100% positive predictive value of fibrinogen less than 2 g/L. Heindl and coworkers[24] previously described the use of fibrinogen concentrate (7–8 g) as a hemostatic agent in patients with major traumatic bleeding refractory to standard coagulation therapy. Lower doses were shown to improve clot formation in acquired hypofibrinogenemia associated with cardiac surgery, liver transplantation, trauma, and placental abruption; in dilutional coagulopathy during complex orthopedic procedures; and in disseminated intravascular coagulation as a result of massive blood loss and transfusion.[25-28] Applying these data to TAAA surgery, we attempted to bring fibrinogen concentration after therapy to a level characteristic for healthy subjects in the same age group as our patients,[13] a level also comparable with the preoperative level, and to see whether this would correct bleeding and reduce the need for allogeneic blood products. The timing of the hemostatic intervention was chosen considering that immediately after CPB with relatively normal duration there would be enough thrombin generation and platelet activity in the patients undergoing TAAA. According to the findings of Hiippala and colleagues,[29] fibrinogen concentration would decrease to 1 g/L at 142% blood loss when replacing blood loss with plasma-poor RBC concentrate, but the critically low levels of all other important coagulation elements (platelets and thrombin-generating coagulation factors, including Factor V) would only be reached after blood loss of more than 200%. Regarding TAAA surgery, additional loss of fibrinogen might be caused by adhesion of fibrinogen and endothelial cells to the inner surface of the graft after suture and perfusion[30] and by bleeding at sutures. At this level, the endogen effect of the plasmatic fibrinogen can be compared with that of exogenous fibrinogen glue.[31]

The platelet count was decreased at the end of CPB. However, even in the presence of thrombocytopenia,

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**TABLE 4. Standard laboratory data in patients undergoing thoracoabdominal aortic aneurysm operations**

| Variable | Allogeneic blood products, group A (n = 12) | Fibrinogen concentrate, group F (n = 6) |
|---|---|---|
| Preoperative | | |
| Hemoglobin (g/dL; normal range, 13.5–17.5 g/dL) | 13.8 ± 1.6 | 12.9 ± 1.1 |
| Hematocrit (%; normal range 41.5%–50.4%) | 39.8 ± 4.1 | 38.1 ± 3.0 |
| PT (s; normal range, 11–13.5 s) | 15.5 ± 4.2 | 14.4 ± 1.0 |
| aPTT (s; normal range 26–35 s) | 30.8 ± 3.6 | 29.5 ± 2.3 |
| Platelet count (1000/μL; normal range 150–450 × 1000/μL) | 219.8 ± 56.1 | 185.7 ± 54.2 |
| Fibrinogen (g/L; normal range, 2.0–4.5 g/L) | 3.8 ± 1.1 | 3.8 ± 1.6 |
| LS time point | | |
| Platelet count (1000/μL) | – | 92.5 ± 37.3 |
| End CPB | | |
| Hemoglobin (g/dL) | – | 9.3 ± 1.0 |
| Hematocrit (%) | – | 27.1 ± 2.8 |
| PT (s) | – | 25.4 ± 2.0 |
| aPTT (s) | – | 42 ± 8.9 |
| Platelet count (1000/μL) | – | 79.2 ± 31.6 |
| Fibrinogen (g/L) | – | 1.6 ± 0.7 |
| After therapy | | |
| Hemoglobin (g/dL) | 10.4 ± 1.4 | 9.8 ± 1.6 |
| Hematocrit (%) | 30.7 ± 3.8 | 28.3 ± 4.6 |
| PT (s) | 17.2 ± 1.3 | 25.8 ± 4.5* |
| aPTT (s) | 33.9 ± 3.4 | 53.7 ± 9.6* |
| Platelet count (1000/μL) | 98.3 ± 24.6 | 79.8 ± 33.0 |
| Fibrinogen (g/L) | 2.5 ± 0.7 | 3.6 ± 1.0* |
| First postoperative day | | |
| Hemoglobin (g/dL) | 10.7 ± 1.0 | 10.3 ± 1.0 |
| Hematocrit (%) | 31.7 ± 3.2 | 30.7 ± 3.1 |
| PT (s) | 17.4 ± 2.8 | 18.1 ± 1.5 |
| aPTT (s) | 36.8 ± 10.0 | 46.2 ± 14.9 |
| Platelet count (1000/μL) | 106.5 ± 30.2 | 94.8 ± 33.7 |
| Fibrinogen (g/L) | 4.4 ± 0.9 | 4.6 ± 1.1 |

Values are presented as the mean ± standard deviation. *PT*, Prothrombin time; *aPTT*, activated partial thromboplastin time; *LS*, last suture (the suture of the last collateral artery on the aortic graft); *CPB*, cardiopulmonary bypass. *Significant difference, group F vs group A: Mann–Whitney *U* test, $P < .05$.

higher levels of fibrinogen can increase the fibrinogen concentration near the platelet surface. A single thrombin molecule efficiently cleaves up to 1680 molecules of fibrinogen,[32] and therefore a low concentration of prothrombin might not represent a limiting factor in clot formation if sufficient fibrinogen is available. High fibrinogen concentration might also compensate for the decreased platelet function in clot formation. There are approximately 40,000 to 80,000 copies of glycoprotein IIb/IIIa receptors on a single activated platelet, and the number of glycoprotein IIb/IIIa receptors on platelets remains relatively constant after CPB.[3] Even in the presence of thrombocytopenia, the extent of platelet–fibrin interactions can be increased by high levels of fibrinogen. This was observed in the present study by the increased EXTEM MCF value after therapy with fibrinogen concentrate. By increasing plasma fibrinogen levels to 3.6 g/L (or 10.7 μmol/L) in vivo, interactions between platelets, thrombin, and fibrinogen appear to be improved. Correlating with this observation, hemostatic therapy with fibrinogen concentrate was more effective than therapy with apheresis platelet transfusion in the presence of thrombocytopenia (platelet count $<30 \times 10^3/mm^3$) in a recent study using the porcine hepatic laceration model.[33]

The decision to treat was not based on laboratory abnormalities of coagulation or bedside testing but on the clinical observation of microvascular bleeding. One safety parameter was represented by the measurement of platelet counts at the time point of the last suture to avoid inadequate transfusion of PCs. However, sufficient correction of bleeding after hemostatic therapy with fibrinogen made transfusion of PCs unnecessary in group F. A second safety parameter was represented by the calculation of the administered fibrinogen dose based on the FIBTEM test because the test offers a prompt readout of both the strength and the stability of the fibrin clot.[26,34] The FIBTEM MCF represents clot strength in the presence of platelet inhibitor cytochalasin D.[34] The method has demonstrated good applicability in the operative setting[26,27] and good correlation to the plasma fibrinogen concentration measured by using the standard laboratory tests.[35] The FIBTEM MCF at the end of CPB was less than the lower limit of the normal range (normal, 9–25 mm) because the plasma fibrinogen concentration was reduced to 1.6 g/L in the prospective group (Table 4). The fibrinogen repletion was guided by FIBTEM testing by using the empiric target MCF of 22 mm. This strategy resulted in an average MCF of 22.7 mm and a mean plasma fibrinogen concentration of 3.6 g/L (Tables 3 and 4). The FIBTEM test was performed in whole blood and required no centrifugation of the sample, a time-consuming step otherwise necessary in the standard laboratory-based assessment of fibrinogen concentration. The decision for a fibrinogen concentrate therapy had to be made within 10 minutes after CPB. The FIBTEM MCF was an ideal parameter for therapy management, being obtained at the point-of-care site approximately 15 minutes after the blood was drawn at the last suture time point. Therefore FIBTEM MCF results were already available when diffuse bleeding was diagnosed.

Calculation of fibrinogen dose based on FIBTEM has not been described in the literature to date. EXTEM analysis, performed both after therapy and 24 hours postoperatively in the ICU, revealed median MCF values of less than 68 mm, the conservative upper limit set to avoid thrombotic complications.[14]

The 2 groups of patients had comparable fibrinogen values on the first postoperative day, suggesting that fibrinogen concentrate therapy of diffuse bleeding after CPB restored the hemostatic potential promptly, but the drug was

used up as substrate for active clot formation and did not remain in circulation long enough to induce significantly higher concentrations on the first postoperative day. It is known that fibrin formation prevents systemic thrombotic events by sequestering thrombin in the forming clot and by reducing the catalytic activity of fibrin-bound thrombin.[36] In agreement with these observations, group F did not present more postoperative thrombotic complications than group A. Notably, the duration of stay in the ICU was also reduced in group F. These findings might be relevant to the assessment of the safety of fibrinogen concentrate administration in this setting. In addition, despite the lower transfusion of RBCs, FFP, and PCs in the fibrinogen therapy group, the laboratory data on hematocrit values, platelet counts, prothrombin time/activated partial thromboplastin time values, and fibrinogen concentrations were comparable between the groups at 24 hours postoperatively, suggesting that FIBTEM-guided fibrinogen therapy was associated with satisfactory correction of hemostasis.

All patients in groups A and F received aprotinin; however, this product is no longer available, and subsequent patients undergoing TAAA operations in our clinic after study completion received tranexamic acid.

The main limitation of the study was that the groups consisted of complete consecutive cohorts and the patients were not randomized to the type of hemostatic therapy received. There were also differences in the preoperative status of patients (eg, more female patients and lower mean body weight in group A), which, although nonsignificant, might have been associated with a higher risk of bleeding. The higher bypass times in the retrospective group, again nonsignificant, might also have had an effect on the hemostatic defects and the associated transfusion requirements in this group. However, group A had higher platelet counts at all times and better posttherapy coagulation parameters, except for fibrinogen plasma concentration. After correction of most coagulation parameters, the retrospective group still required significantly higher transfusion while in the ICU based on the drainage volume and the persistent blood loss.

Our findings indicate that coagulation therapy with fibrinogen concentrate might reduce the high use of allogeneic blood products and postoperative bleeding in patients undergoing TAAA surgery. To our knowledge, this was the first time that a fibrinogen level of 3.6 g/L, in the higher normal range, was targeted. The FIBTEM MCF appeared to be an appropriate parameter for dosage of fibrinogen concentrate. The clinical value of these data is limited by the low number of patients and the nonrandomized study design. However, the data are encouraging and suggest that this hypothesis should be examined in a prospective, randomized, double-blind, placebo-controlled clinical trial in this setting.

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