Effects of Fibrinogen Concentrate as First-line Therapy during Major Aortic Replacement Surgery

A Randomized, Placebo-controlled Trial

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ABSTRACT

Background: Fibrinogen is suggested to play an important role in managing major bleeding. However, clinical evidence regarding the effect of fibrinogen concentrate (derived from human plasma) on transfusion is limited. The authors assessed whether fibrinogen concentrate can reduce blood transfusion when given as intraoperative, targeted, first-line hemostatic therapy in bleeding patients undergoing aortic replacement surgery.

Methods: In a placebo-controlled randomized trial including patients (n = 61) undergoing aortic replacement surgery under cardiopulmonary bypass, the transfusion of allogeneic blood components was significantly reduced in the fibrinogen concentrate group (median 2 vs. 13 U; P < 0.001)

Results: Twenty-nine patients in the fibrinogen concentrate group and 32 patients in the placebo group were eligible for the efficacy analysis. During the first 24 h after administration of study medication, patients in the fibrinogen concentrate group received fewer allogeneic blood components than did patients in the placebo group (median, 2 vs. 13 U; P < 0.001; primary endpoint). Total avoidance of transfusion was achieved in 13 (45%) of 29 patients in the fibrinogen concentrate group, whereas 32 (100%) of 32 patients in the placebo group received transfusion (P < 0.001). There was no observed safety concern with using fibrinogen concentrate during aortic surgery.

What We Already Know about This Topic

- Although fibrinogen plays an important role in hemostasis, clinical evidence regarding the effect of administering fibrinogen concentrate remains limited

What This Article Tells Us That Is New

- In a placebo-controlled randomized trial including patients (n = 61) undergoing aortic replacement surgery under cardiopulmonary bypass, the transfusion of allogeneic blood components was significantly reduced in the fibrinogen concentrate group (median 2 vs. 13 U; P < 0.001)

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Conclusions: Hemostatic therapy with fibrinogen concentrate in patients undergoing aortic surgery significantly reduced the transfusion of allogeneic blood products. Larger multicenter studies are necessary to confirm the role of fibrinogen concentrate in the management of perioperative bleeding in patients with life-threatening coagulopathy.

Major bleeding during complex surgery increases the need for blood transfusions, prolongs the patient’s stay in the intensive care unit (ICU), and is associated with increased morbidity and mortality.\(^1\)\(^,\)\(^2\) The standard treatment of perioperative bleeding involves the transfusion of allogeneic blood components (erythrocytes, fresh frozen plasma [FFP], platelet concentrate, or cryoprecipitate). Although these components have become safer, there is evidence that the transfusion of allogeneic blood components may be associated with a risk of serious adverse events.\(^3\)\(^,\)\(^4\) Thus, treatment approaches that can reduce transfusion appear desirable.

Clot strength increases with increasing concentrations of fibrinogen, and fibrinogen levels higher than 200 mg/dl have been suggested for optimal clot formation.\(^6\)\(^,\)\(^8\) Immediately after cardiopulmonary bypass (CPB), fibrin formation is impaired to a greater extent than either thrombin generation or the platelet component of clot strength.\(^9\) The plasma concentration of fibrinogen\(^10\)\(^,\)\(^11\) and the firmness (elasticity/strength) of the fibrin-based clot\(^1\)\(^2\) have been reported to decrease by an average of 34–42% in response to CPB. Furthermore, low levels of fibrinogen are associated with an increased risk of postoperative bleeding.\(^10\)\(^,\)\(^11\)\(^,\)\(^12\)\(^,\)\(^13\)

Our group has developed and validated a model for individualized dosing of fibrinogen concentrate,\(^17\)\(^,\)\(^18\) by measuring firmness of the fibrin-based clot, which is mainly dependent on plasma fibrinogen levels.\(^13\)\(^,\)\(^21\)\(^,\)\(^22\) Maximum clot firmness (MCF) of the fibrin-based clot can be monitored using a commercially available fibrin-based thromboelastometry test (FIBTEM).\(^11\)\(^,\)\(^23\)

A clinical study is needed to investigate the efficacy and safety of fibrinogen concentrate in managing severe perioperative bleeding. We hypothesized that fibrinogen concentrate can reduce the need for blood transfusions without increasing the rate of serious adverse events when given intraoperatively as individualized first-line hemostatic therapy in bleeding patients undergoing aortic replacement surgery.

Materials and Methods

Study Design and Population

This phase 2, prospective, randomized, double-blind, placebo-controlled, parallel-group, stratified, clinical study was conducted at a single center (Hannover Medical School, Hannover, Germany). It was approved by the Local Ethics Committee in Hannover, Germany, and by the German Regulatory Authorities; it was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was assigned Local Ethics Committee reference code no. 4891M-mono, EudraCT trial no. 2007-004612-31, and ClinicalTrials.gov identifier no. NCT00701142.

Patients aged 18 yr or older for whom elective aortic replacement surgery involving CPB was planned and who provided signed informed consent were enrolled between June 2008 and April 2010. All aortic valve operations with root/ascending aorta replacement (thoracic aortic aneurysm [TAA]), with or without aortic arch replacement, and thoracoabdominal replacements were eligible. Patients were excluded from the study if they had undergone previous surgery at the same aortic site, if they had a congenital or acquired coagulation disorder, if they had a myocardial infarction or stroke in the previous 2 months, or if they used aspirin, clopidogrel, or vitamin K antagonists in the previous 2–5 days. All patients received antifibrinolytic prophylaxis with tranexamic acid (30 mg/kg bodyweight as a preoperative loading dose, followed by 1 mg/kg bodyweight/h throughout surgery). CPB was established after aortic cannulation and administration of 400 IU/kg heparin (Heparin-Natrium-25000-ratiopharm®; Merckle GmbH, Blaubeuren, Germany).

Procedures

Before surgery, patients were randomized to receive either fibrinogen concentrate or placebo; study medication was administered if clinically relevant bleeding occurred. This was defined as a 5-min bleeding mass of 60–250 g immediately after removal from CPB, neutralization of heparin with protamine sulfate (Protamin Valeant, Valeant Pharmaceuticals GmbH, Eschborn, Germany; protamine–heparin ratio of 1:1), and completion of surgical hemostasis, which includes suture placement and electrocautery (or diathermy) (fig. 1). Completion of surgical hemostasis consisted of surgical control of focal bleeding. Surgical hemostasis was deemed to be complete if no obvious sources of bleeding were identified. A 5-min bleeding mass was subsequently determined by weighing dry surgical cloths and compresses, applying them to the surgical area for 5 min and weighing them again. No irrigation of the operative field was performed during the measurement of bleeding mass. Bleeding mass in the range 60–250 g was considered to be clinically relevant and coagulopathic in nature; an upper limit was included because of the life-threatening nature of massive bleeding. The thresholds of 60 and 250 g were chosen based on clinical experience at the authors’ center.\(^17\)\(^,\)\(^18\) Randomized patients not eligible for treatment or withdrawn from the study before 24 h after the administration of study medication were replaced until there were sufficient patients to provide primary efficacy endpoint data for each study arm. Stratification was done according to surgery type (thoracoabdominal aortic aneurysm or TAA).
Fig. 1. Treatment algorithm and study design. Flowchart showing details of clinical steps, assessments performed, and treatments administered throughout the study. AE = adverse event; CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; HRQoL = health-related quality of life; SAE = serious adverse event. * Standard control step to ensure no obvious sources of surgical bleeding.
Study medication was prepared in 50-ml opaque syringes by the pharmacist, according to a randomization code generated by the contract research organization (Accovion GmbH, Eschborn, Germany) using SAS (SAS Institute, Cary, NC) (the investigator initially assigned a randomization number to each patient). The randomization ratio of the treatment arms in each stratum (thoracoabdominal aortic aneurysm and TAA) was 1:1, with a block size of 4. Each 50-ml syringe contained either 1 g fibrinogen concentrate (Haemocomplettan P®, RiaSTAP™; CSL Behring, Marburg, Germany) diluted in 50 ml sterile water, or an equivalent volume of 0.9% saline as placebo. The medication was delivered to the operation room upon request of the study investigator (anesthesiologist) and administered intravenously within 5 min of bleeding measurement. In order for study medication to be administered, patients had to fulfill the following conditions: activated clotting time less than 150 s, body temperature higher than 36°C, pH more than 7.3, and hemoglobin level higher than 8.5 g/dl. To ensure blinding, only the pharmacist had access to the randomization code; the use of opaque syringes ensured that fibrinogen concentrate and placebo were visually identical.

Doses were determined from the MCF of the FIBTEM test, using a model developed in previous studies for individualizing fibrinogen concentrate dosing.\(^\text{17,18}\) The FIBTEM test was performed by point-of-care thromboelastometry (ROTEM\textsuperscript{TM} device; TEM International, Munich, Germany), using blood samples taken 20 min before the end of CPB. The time taken to obtain the MCF value was 15 min. The fibrinogen concentrate dose was calculated by the unblinded point-of-care laboratory staff as follows: Fibrinogen concentrate dose (g) = (target FIBTEM MCF – actual FIBTEM MCF) (mm) × (bodyweight [kg] / 70) × 0.5 g/mm.\(^\text{11,17,18}\) The target FIBTEM MCF was 22 mm. None of the blinded personnel (investigator and staff of the operating room and ICU) had access to FIBTEM or fibrinogen concentration values after the administration of study medication.

Approximately 5 min after the administration of study medication, bleeding mass was measured again. A transfusion algorithm was initiated in patients with a bleeding mass of 60–250 g as follows: if, upon removal of the aortic clamp, platelet count was lower than 100,000/µl, 2 U of apheresis platelet concentrate was administered; if platelet count was 100,000/µl or higher, 4 U FFP was administered in approximately 10 min. Subsequently, 5-min bleeding mass was reevaluated. If clinically relevant bleeding continued, the patient was given the blood component (platelet concentrate/FFP) not administered after the first bleed, and 5-min bleeding mass was again measured. Transfusion packages of 1 U platelet concentrate and 2 U FFP were administered until the 5-min bleeding mass was less than 60 g. Upon completion of hemostatic therapy, the thorax was closed (last suture = end of surgery), and the patient was transferred to the ICU. In the event of blood drainage higher than 400 ml during 1 h in the ICU, 1 U platelet concentrate and 2 U FFP were administered. Erythrocytes were also administered after CPB to maintain a hemoglobin level higher than 8.5 g/dl. Fibrinogen levels were measured using the Clauss assay, before and after the administration of study medication.

**Study Endpoints**

The primary endpoint was the total number of units of allogeneic blood components (erythrocytes plus FFP plus platelet concentrate) given to patients between the administration of study medication and 24 h thereafter. Secondary endpoints included the number of units of each individual allogeneic blood component given (erythrocytes, FFP, and platelet concentrate), the proportion of patients who received no allogeneic blood components (total avoidance), the number of days not in the ICU or hospital during the 45 days after surgery (assumed to be zero for patients dying within that period), and mortality at 45 days after surgery.

Safety was assessed principally by treatment-emergent adverse events occurring within 10 days of treatment. The follow-up period for serious adverse events was 45 days. Patients were monitored for viral seroconversion by hepatitis A virus, hepatitis B virus, hepatitis B core, hepatitis B surface antigen, hepatitis C virus, human immunodeficiency virus 1 and 2, and parvovirus B19 testing (enzyme immunoassays and polymerase chain reaction were used). In accordance with Good Clinical Practice, the study sponsor evaluated safety data throughout the study.

**Statistical Analysis**

Sixty patients were planned for the primary endpoint based on an assumed difference between the treatment group means of 4.25 ± 5.3 U (where 5.3 is the SD) with a two-sided type I error rate of 5% and more than 80% power for the nonparametric Wilcoxon rank sum test. These assumptions were derived from a previously reported average transfusion of 8.5 ± 5.3 U during TAA surgery.\(^\text{17}\) We assumed that the use of fibrinogen concentrate would reduce transfusion of allogeneic blood products by 50% compared with the standard-of-care group. The efficacy and safety analyses included all patients who were randomized and received study treatment. This was not strictly an intention-to-treat analysis because of the need to randomize patients before ascertaining whether they met the study inclusion criteria (if randomization had been performed after establishing that patients met the study inclusion criteria, hemostatic therapy would have been delayed unethically).

Inferential testing of the primary efficacy endpoint was based on a nonparametric Wilcoxon rank sum test with a two-sided type I error rate of 5%, testing the null hypothesis of no difference between the treatment groups. An unstratified Hodges–Lehman point estimate and the corresponding two-sided 95% CI for the treatment difference were also calculated. The primary endpoint was found to have a positively skewed nonnormal distribution. The proportion of patients receiving no allogeneic blood components within the first 24 h after start of infusion of study medication was analyzed in an exploratory manner applying a chi-square test.
Exploratory analysis was performed for selected secondary endpoints (24-h transfusion of erythrocytes, FFP, and platelet concentrate [each component analyzed separately]). Additional analyses were performed for fibrinogen and hemoglobin using the two-sample \( t \) test for normally distributed outcomes and the Wilcoxon rank sum test for outcomes with a skewed distribution.

All other secondary efficacy endpoints were analyzed by descriptive statistics, with values typically presented as mean ± SD. For the between-group comparison of safety outcomes, risk ratios with 95% CIs were calculated where possible (nonzero incidence).

Data for the main efficacy endpoints are presented as median (with interquartile range, between the 25th and the 75th percentiles) values because the data were not normally distributed. SAS version 9.1.3 (SAS Institute) was used for all of the statistical analyses, except the Wilcoxon rank sum test, which was performed using StatXact (version 8.1; Cytel, Cambridge, MA).

Results

Patient Disposition

Of 80 patients screened, 61 were randomized and treated (fig. 2). Of these, 18 patients underwent thoracoabdominal aortic aneurysm surgery, 22 underwent TAA with arch surgery, and 21 underwent TAA without arch surgery (table 1). The two treatment groups had similar perioperative
characteristics, and the population was typical for patients undergoing aortic surgery (table 1). Preoperative mean ± SD FIBTEM MCF was 17.9 ± 6.1 mm in the fibrinogen concentrate group and 16.4 ± 3.8 mm in the placebo group.

**Dose of Study Medication**

On the basis of MCF values from the FIBTEM test performed during CPB, a median dose of 8 g (interquartile range [IQR], 6–9 g) of fibrinogen concentrate was administered to patients in the fibrinogen concentrate group (median volume, 400 ml; IQR, 300–450 ml). The median volume of study medication administered to the placebo group was also 400 ml (IQR, 300–450 ml). These doses were calculated from the FIBTEM MCF of samples taken approximately 20 min before removal from CPB; the mean MCF was 9.7 ± 3.1 mm in the fibrinogen concentrate group and 9.5 ± 2.7 mm in the placebo group. As shown in table 1, the two study groups were also comparable immediately before the administration of study medication (after removal from CPB, administration of protamine, and completion of surgical hemostasis), in terms of 5-min bleeding mass and activated clotting time.

<table>
<thead>
<tr>
<th>Table 1. Patients’ Characteristics and Perioperative Data (Fibrinogen Concentrate, N = 29; Placebo, N = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen Concentrate</td>
</tr>
<tr>
<td>Males, n (%)</td>
</tr>
<tr>
<td>Females, n (%)</td>
</tr>
<tr>
<td>Age, mean ± SD, yr</td>
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<tr>
<td>Weight, mean ± SD, kg</td>
</tr>
<tr>
<td>Body mass index, mean ± SD, kg/m²</td>
</tr>
<tr>
<td>Obesity (body mass index &gt;30 kg/m²), n (%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
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<tr>
<td>Previous myocardial infarction, n (%)</td>
</tr>
<tr>
<td>Previous heart operation, n (%)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
</tr>
<tr>
<td>Preoperative data</td>
</tr>
<tr>
<td>FIBTEM MCF, mean ± SD, mm</td>
</tr>
<tr>
<td>Plasma fibrinogen concentration, mean ± SD, mg/dl</td>
</tr>
<tr>
<td>Hemoglobin concentration, mean ± SD, g/dl</td>
</tr>
<tr>
<td>Platelet count, median (IQR), ×10⁹/l</td>
</tr>
<tr>
<td>aPTT, median (IQR), s</td>
</tr>
<tr>
<td>PT, median (IQR), s</td>
</tr>
<tr>
<td>Antithrombin, median (IQR), %</td>
</tr>
<tr>
<td>Operation data</td>
</tr>
<tr>
<td>CPB time, mean ± SD, min</td>
</tr>
<tr>
<td>Operation type TAAA, n (%)</td>
</tr>
<tr>
<td>Operation type TAA with arch, n (%)</td>
</tr>
<tr>
<td>Operation type TAA without arch, n (%)</td>
</tr>
<tr>
<td>5-min bleeding mass before administration of study medication, mean ± SD, g</td>
</tr>
<tr>
<td>Activated clotting time before administration of study medication, mean ± SD, s</td>
</tr>
<tr>
<td>Postoperative outcome data</td>
</tr>
<tr>
<td>ICU-free time during first 45 days postoperatively, median (IQR), days</td>
</tr>
<tr>
<td>Hospitalization-free time during first 45 days postoperatively, median (IQR), days</td>
</tr>
<tr>
<td>Blood drainage volume between last suture and 24 h after study medication, median (IQR), ml</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, median (IQR), or absolute and percentage frequency.

* One patient died during the 45-day period; a value of zero was attributed to this patient for ICU- and hospitalization-free time.
† Four patients died during the 45-day period; a value of zero was attributed to these patients for ICU- and hospitalization-free time.

aPTT = activated partial thromboplastin time; CPB = cardiopulmonary bypass; FIBTEM = fibrin-based thromboelastometry test; ICU = intensive care unit; IQR = interquartile range; MCF = maximum clot firmness; N = total number of patients; n = number of patients in given category; PT = prothrombin time; TAA = thoracic aortic aneurysm; TAAA = thoracoabdominal aortic aneurysm.
During the 24-h period after start of study medication, patients treated with fibrinogen concentrate received fewer units of allogeneic blood components (median, 2 U; IQR, 0–8 U) than patients treated with placebo (median, 13 U; IQR, 8–21 U); the treatment difference (−9 U; 95% CI, −13 to −6 U) was statistically significant (P < 0.001, table 2). A sensitivity analysis was performed, excluding patients who dropped out within 24 h of the administration of study medication (one patient in the placebo group). This showed a similar treatment difference (−8 U; 95% CI, −13 to −6 U).

The treatment difference was also generally similar for each of the aortic replacement procedures included in the study. The number of units of erythrocytes, FFP, and platelet concentrate administered during the 24 h after start of study medication was lower in the fibrinogen concentrate group than that in the placebo group (table 2). There was no between-group difference in hemoglobin at any time point (table 3). Numbers of ICU-free days and hospital-free days were also similar in the two study groups (table 1).

### Safety

Similar proportions of patients in each treatment group reported treatment-emergent adverse events (relative risk, 1.0; table 4). The majority of treatment-emergent adverse events reported were typical for patients undergoing cardiac surgery, the most common ones being pleural effusion and atrial fibrillation. None of the treatment-emergent adverse events reported in the study was considered to be related to study medication, and none led to discontinuation from the study. Reoperation because of persistent bleeding was undertaken in four patients in the fibrinogen concentrate group and four patients in the placebo group. Although this constituted a relative risk of 4.4, there was no significant between-group difference. In all five patients, a surgical source of bleeding was identified during reoperation. The incidence of serious adverse events was similar in both study groups (relative risk, 1.1). More serious adverse events led to death in the placebo group versus...
the fibrinogen concentrate group (four patients vs. one patient, respectively). Although the relative risk was 0.3, there was no significant between-group difference. None of the serious adverse events was considered related to study medication. Cardiorespiratory arrest (day 1) and later death due to brain herniation and myocardial infarction (day 28) were reported in a 77-yr-old fibrinogen concentrate patient with a previous history of myocardial infarction, coronary angioplasty, and obesity who underwent repair of TAA and arch. Cardiorespiratory arrest was reported while the patient was being transferred for a computed tomography scan with unstable respiratory status. Resuscitation was successful.

Except for this patient, no potentially thromboembolic events were reported in the fibrinogen concentrate group. In the placebo group, two thromboembolic events were reported (one pulmonary embolism and one air embolism). There were no viral transmissions in either study group.

**Discussion**

This study demonstrates that fibrinogen concentrate, administered intraoperatively as targeted first-line hemostatic intervention, reduces the need for transfusion of allogeneic blood products in patients undergoing complex aortic surgery. The median transfusion of allogeneic blood components was reduced by 85% among patients receiving fibrinogen concentrate (2 U transfused) compared with placebo (13 U transfused). Total avoidance of allogeneic blood components in 13 of 29 patients (45%) treated with fibrinogen concentrate.

### Table 3. Changes in Fibrinogen and Hemoglobin Levels over Time (Fibrinogen Concentrate, N = 29; Placebo, N = 32)

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Fibrinogen Concentrate</th>
<th>Placebo</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, mg/dl, plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>304 ± 99</td>
<td>289 ± 63</td>
<td>16 (~26 to 58)</td>
</tr>
<tr>
<td>20 min before removal of CPB</td>
<td>166 ± 38</td>
<td>161 ± 36</td>
<td>5 (~14 to 24)</td>
</tr>
<tr>
<td>Immediately after removal from CPB (before administration of study medication)</td>
<td>157 ± 40</td>
<td>155 ± 40</td>
<td>~2 (~18 to 23)</td>
</tr>
<tr>
<td>At time of last suture (i.e., end of surgery, after administration of study medication)</td>
<td>260 ± 48</td>
<td>189 ± 34</td>
<td>70 (49 to 91)*</td>
</tr>
<tr>
<td>1 day after surgery</td>
<td>343 ± 74</td>
<td>333 ± 54†</td>
<td>10 (~24 to 43)</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before surgery</td>
<td>12.5 ± 1.3</td>
<td>13.2 ± 1.3</td>
<td>~0.6 (~1.3 to 0.0)</td>
</tr>
<tr>
<td>20 min before removal of CPB</td>
<td>9.4 ± 1.0</td>
<td>9.6 ± 1.1</td>
<td>~0.2 (~0.8 to 0.3)</td>
</tr>
<tr>
<td>Immediately after removal from CPB</td>
<td>9.7 ± 0.9</td>
<td>10.0 ± 0.9</td>
<td>~0.3 (~0.8 to 0.2)</td>
</tr>
<tr>
<td>At time of last suture</td>
<td>10.0 ± 1.1</td>
<td>9.7 ± 1.6</td>
<td>0.3 (~0.4 to 1.0)</td>
</tr>
<tr>
<td>1 day after surgery</td>
<td>10.4 ± 1.1</td>
<td>10.1 ± 0.9‡</td>
<td>0.3 (~0.2 to 0.9)</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD, except “difference,” which is presented as mean (95% CI).

* Statistically significant difference between groups (P < 0.001), † n = 31 (data unavailable for one patient who died within 24 h), ‡ n = 30 (hemoglobin data were unavailable at this time point for two patients, including one who died within 24 h).

CPB = cardiopulmonary bypass.

### Table 4. Major Safety Endpoints (Fibrinogen Concentrate, N = 29; Placebo, N = 32)

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Fibrinogen Concentrate</th>
<th>Placebo</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs (10-day follow-up)</td>
<td>24 (83%)</td>
<td>27 (84%)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>SAEs (45-day follow-up)</td>
<td>5 (17%)</td>
<td>5 (16%)</td>
<td>1.1 (0.4–3.4)</td>
</tr>
<tr>
<td>SAEs leading to death</td>
<td>1 (3%)</td>
<td>4 (13%)</td>
<td>0.3 (0.0–2.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (3%)*</td>
<td>0</td>
<td>NC</td>
</tr>
<tr>
<td>Cardiorespiratory arrest</td>
<td>0</td>
<td>1 (3%)</td>
<td>NC</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>0</td>
<td>1 (3%)</td>
<td>NC</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>0</td>
<td>1 (3%)</td>
<td>NC</td>
</tr>
<tr>
<td>Operative hemorrhage</td>
<td>0</td>
<td>1 (3%)</td>
<td>NC</td>
</tr>
<tr>
<td>Reoperation because of surgical bleeding</td>
<td>4 (14%)</td>
<td>4 (13%)</td>
<td>1.1 (0.3–4.0)</td>
</tr>
<tr>
<td>Viral transmissions</td>
<td>0</td>
<td>0</td>
<td>NC</td>
</tr>
</tbody>
</table>

Data are presented as n (%) of patients, except for relative risk, which is presented with the 95% CI in parentheses.

* Reported as follow-up TEAE, 28 days after infusion of fibrinogen concentrate; cause of death was brain herniation and myocardial infarction.

N = total number of patients; NC = not calculated; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
is of high clinical relevance, considering that all patients in
the placebo group received allogeneic blood components.

These outcomes may be attributable to plasma fibrinogen
concentration being raised more quickly and to higher
levels among patients receiving fibrinogen concentrate
compared with those who received placebo. The use of
fibrinogen concentrate instead of allogeneic blood products
has important clinical implications. Fibrinogen concentrate
is immediately available for reconstitution, with no need
for thawing or blood group matching, and has a low
administration volume. It can therefore be administered in
less time than either FFP or cryoprecipitate, decreasing the
time to control bleeding. In the context of severe bleeding,
the administration of 6 g fibrinogen concentrate in 1–2 min
has been reported feasible. In contrast, FFP administration
causes hemodilution, and the concentration of fibrinogen
in FFP (approximately 200 mg/dl) limits the extent to
which fibrinogen levels can be increased. Cryoprecipitate
provides a considerably higher concentration of fibrinogen
(300–600 mg in 20–50 ml, corresponding to a range of
600–3000 mg/dl), but this concentration is more variable
than with fibrinogen concentrate, meaning that doses
cannot be controlled as accurately. In addition, as with
FFP, blood group matching is required before administering
cryoprecipitate. The use of fibrinogen concentrate along with
other coagulation factor concentrates such as prothrombin
complex concentrate, in the context of a treatment algorithm
based on viscoelastic point-of-care coagulation testing,
was recently shown to decrease blood transfusion and
thrombotic events among cardiovascular surgery patients.
This approach is of particular interest because it enables the
comprehensive treatment of coagulopathy using coagulation
factor concentrates, with the potential for larger reductions
in allogeneic blood transfusions than can be achieved with
fibrinogen alone.

Postoperative data show that the increase in fibrinogen
levels, relative to the placebo group, was only transitory (less
than 24 h), and this may be viewed positively from a safety
perspective. The safety profile of fibrinogen concentrate was
similar to that of placebo. This study was not designed to
detect differences between fibrinogen concentrate and pla-
cebo in morbidity or mortality. Nevertheless, the lack of
conclusive between-group differences in safety is consistent
with the previously reported safety of fibrinogen concentrate,
including a very low risk of thromboembolic complications
and an excellent margin of virus safety. Four patients in
the fibrinogen concentrate group underwent reoperation
compared with one in the placebo group. Surgical bleeding
was identified in all five of these cases. In general, the pos-
sible reasons for reoperation are multifactorial, and there is
no indication in this study that the reasons were related to
study medication. The reoperation data are inconsistent with
the overall reduction in the use of allogeneic blood products
in the fibrinogen concentrate group. Importantly, all allo-
geneic blood products administered within 24 h of study
medication were included in the primary endpoint, includ-
ing those used during and after reoperation, and all patients
left the operating room with a 5-min bleeding mass less than
60 g.

This is the largest randomized, double-blind, placebo-
controlled study of fibrinogen concentrate therapy. It is
the first such study of fibrinogen concentrate administered
intraoperatively as first-line hemostatic therapy, and the first
placebo-controlled study of fibrinogen concentrate among
patients undergoing complex cardiovascular surgery. Only
two previous prospective randomized clinical studies of
fibrinogen concentrate have been performed. The first
one, patients undergoing cystectomy (n = 20) with blood
loss substituted by hydroxethyl starch exhibited a significant
increase in MCF after fibrinogen supplementation (45 mg/
kg) versus placebo. Transfusion and blood loss were similar
in the two groups during surgery, whereas erythrocytes were
administered to eight patients in the placebo group versus
two in the fibrinogen group postoperatively (P < 0.05). The
second study, performed in 20 coronary bypass graft patients,
showed that the preoperative, prophylactic administration
of fibrinogen concentrate (2 g) reduced blood loss by 32%
(P = 0.010). Blood transfusions were undertaken in one
patient in the fibrinogen group compared with three in
the placebo group. The present study cohort was relatively
homogeneous, and the different types of operation were
equally distributed between the two treatment groups,
ensuring that they were comparable. Assessments such as
fibrinogen concentration and prothrombin time confirm the
comparability of the two groups before the administration
of study medication. By administering study medication
intraoperatively, patients received study medication during a
period when, if treatment consisted only of allogeneic blood
products, the patient would only have been monitored while
blood products are prepared. Consequently, this placebo-
controlled study may also be considered as a comparison of
fibrinogen concentrate with standard hemostatic treatment
based on FFP and platelet concentrate.

Dosing in our study was based on viscoelastic point-
of-care coagulation testing to obtain results more quickly
than standard laboratory parameters. Bleeding manage-
ment guidelines are beginning to advocate the use of visco-
elastic methods. However, consideration is required as
to which viscoelastic methods are used: recent data showed
that simultaneous performance of several ROTEM assays
test (e.g., INTEM, EXTEM, FIBTEM, and HEPTEM) is bet-
ter able to distinguish different coagulopathies than a sin-
gle kaolin-activated thrombelastography assay. FIBTEM
is a viscoelastic test designed to measure firmness of a clot
formed in the presence of a platelet inhibitor (i.e., fibrin-
Based clot firmness). Importantly, FIBTEM does not provide
a measurement of fibrinogen concentration. Firm-
ness of the fibrin-based clot is measured in SI units (Système
International d’Unités) that are completely different from
those of fibrinogen concentration (dyne/cm² or gigapascal,
as opposed to g/l or mol/l). Nevertheless, studies have shown correlation between FIBTEM MCF and measurements of fibrinogen concentration. The aim was to restore FIBTEM MCF to 22 mm, higher than the mean preoperative baseline level of 16–18 mm and at the high end of the normal range (9–25 mm). This target was chosen to allow fibrinogen concentrate to be effective as a pharmacological hemostatic agent. There is evidence that fibrinogen deficiency is the primary problem associated with hemodilution, and that fibrinogen supplementation may compensate for reduced platelet levels. Twenty-two millimeters typically corresponds to a fibrinogen level of approximately 360 mg/dl, which is within the normal range of 163–458 mg/dl and similar to the normal value of 330 mg/dl reported for patients older than 60 yr. Historically, the threshold plasma concentration for fibrinogen supplementation was set at 100 mg/dl. Newer recommendations give this threshold as more than 150 mg/dl. A higher target may be appropriate because clot firmness continues to increase with fibrinogen concentration throughout the normal range.

The present study has several limitations. Our analysis does not strictly meet the definition for intention to treat. To avoid delaying treatment, patients were randomized to treatment before the presence of clinically significant coagulopathic bleeding was determined. Selection bias was not introduced because patients’ entry to the study was based on predefined, objective criteria as opposed to clinical judgment, and because the criteria were the same for both study groups. The use of 5-min bleeding mass as a study inclusion criterion and as a trigger for the transfusion of allogeneic blood products provides an objective assessment of bleeding rate, but the authors recognize that it is not the current standard trigger for hemostatic intervention and that it may not be applicable in all clinical settings. However, we are confident this method allowed accurate and reproducible measurement of blood loss in the present setting. Patients with preoperative coagulation disorders or anticoagulation therapy were excluded, meaning that the applicability of the results to such patients may be limited. However, homogeneity of the study cohort was increased, enhancing comparison of the two treatment groups. This study is also limited by its small sample size and use of a single center. Therefore, the robust assessment of safety (i.e., low-frequency adverse events) is not possible. However, the sample size was determined statistically from an assumption that the use of allogeneic blood products would be reduced by 50%, a reduction of clinical and practical relevance. Also, while the use of a single center may limit applicability to other centers, it will also have reduced variability in personnel and clinical procedures. There is now a need for further studies of fibrinogen concentrate in different surgical fields, in patients with different preoperative conditions, and in larger numbers of patients to analyze factors that may influence efficacy and to confirm the observed safety profile. Ideally, such studies would be randomized and controlled with true intention-to-treat analysis, while also remaining ethical.

In conclusion, this study in patients undergoing aortic replacement surgery has shown that targeted first-line treatment with fibrinogen concentrate is able to reduce the transfusion of allogeneic blood products. If confirmed in larger, multicenter studies, fibrinogen concentrate administration would provide a concrete means of reducing or eliminating transfusions. Consequently, this therapeutic approach has the potential to change the treatment paradigm for perioperative bleeding in patients with potentially life-threatening coagulopathy.

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