Does Intraoperative Fibrinogen Affect Blood Loss or Transfusion Practice After Aortic Arch Surgery: A Prematurely Ended Randomized Trial

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Abstract

Cardiovascular surgery is often complicated by significant bleeding due to perioperative coagulopathy. The effectiveness of treatment with fibrinogen concentrate to reduce the perioperative blood transfusion rate after thoracic aortic replacement surgery in prior studies has shown conflicting results. Therefore, we conducted a double-blind randomized controlled trial to investigate if a single dose of intraoperative fibrinogen administration reduced blood loss and allogeneic transfusion rate after elective surgery for thoracic arch aneurysm with deep hypothermic circulatory arrest. Twenty patients were randomized to fibrinogen concentrate ($N = 10$) or placebo ($N = 10$). The recruitment of study patients was prematurely ended due to a low inclusion rate. Perioperative transfusion, 5-minute bleeding mass after study medication and postoperative blood loss were not different between the groups with fibrinogen concentrate or placebo. Due to small volumes of postoperative blood loss and premature study termination, a beneficial effect of fibrinogen concentrate on the number of blood transfusions could not be established. However, treatment with fibrinogen efficiently restored fibrinogen levels and clot strength to preoperative values with a more effective preserved postoperative thrombin generation capacity. This result might serve as a pilot for further multicenter studies to assess the prospective significance of automated and standardized thrombin generation as a routine assay for monitoring perioperative coagulopathy and its impact on short- and long-term operative results.

Keywords

hemostasis, fibrinogen, thrombin generation, thromboelastography, transfusion, thoracic aorta surgery

Introduction

Aortic replacement surgery is often complicated by significant bleeding due to perioperative coagulopathy. Consumption and dilution of clotting factors, inflammation and fibrinolysis, use of deep hypothermia with circulatory arrest (HCA) and long cardiopulmonary bypass (CPB) time increase the need for blood transfusions to treat perioperative blood loss.[1] Although blood transfusion is increasingly safe, evidence suggests that it remains associated with adverse clinical outcomes.[2] To reduce the risk of transfusion associated complications, perioperative coagulopathy can be treated with coagulation factor replacement therapies, but adequate powered randomized studies on the efficacy and safety of such therapies are scarce.[3,4]

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Plasma fibrinogen plays an important role in perioperative hemostasis, but is often reduced to low concentrations during cardiac surgery.[5] Low plasma fibrinogen levels reduce clot firmness and have been associated with bleeding complications.[6] Plasma fibrinogen initiates clot formation and enhances platelet aggregation by binding platelet glycoprotein IIb/IIIa receptors found on platelets.[7,8] To prevent depleted plasma fibrinogen levels, cardiac surgery patients can be substituted by plasma transfusion, fibrinogen concentrate (FC) or cryoprecipitate. Transfusion with plasma immediately supplies all essential coagulant factors, but requires large volumes to restore plasma fibrinogen levels, with risk of circulatory overload.

Data regarding the effectiveness of treatment with FC to reduce perioperative blood transfusion in aortic replacement surgery in prior studies have shown conflicting results. A landmark randomized trial in 2013 showed that blood transfusion was significantly reduced by FC compared to placebo.[9] However, a follow-up multicenter study in 2016 could not confirm these results.[10] FC did not reduce blood loss in studies that included a cardiac surgery population with lower bleeding risk (ie, <20% of included patients had aortic replacement surgery).[11] We therefore conducted a double-blind randomized controlled trial in patients scheduled for aortic arch replacement surgery with the use of HCA to investigate if intraoperative FC administration reduced the need for allogeneic blood transfusion within 24 hours after surgery.

Patients and Methods

Study Design

A randomized, placebo-controlled, double-blind, clinical trial of FC (Hemocomplettan P, CSL Behring, Marburg) versus placebo for treatment of post-CPB coagulopathy in patients undergoing elective aorta replacement surgery with HCA for thoracic aneurysm at a large tertiary hospital for cardiac surgery. Ethical approval was provided by the local ethics committee (Medical Ethics Research Committee United, no. NL45370.020.13) on July 16, 2014. The study protocol was registered at the US National Library of Medicine (NCT02299947) and performed in accordance with the Declaration of Helsinki. All patients gave written informed consent prior to entering the study. On July 2015 the protocol was amended after a serious adverse event (one patient died of mesenteric ischemia) and a history of severe atherosclerosis or type B aortic dissection was added to the exclusion criteria. Due to a low inclusion rate, the study was discontinued prematurely.

Study Population

Adults with thoracic aneurysm scheduled for aortic replacement surgery were eligible for study participation. Patients with the following medical conditions were not recruited: prior thrombosis or myocardial infarction, congenital coagulation disorder, use of antiplatelet therapy or vitamin K antagonists within 5 days preceding surgery, a history of severe atherosclerosis or type B aortic dissection, prior thoracic surgery, pregnancy and preoperative fibrinogen concentration <1 g/l. Patients were informed by telephone at least 1 week prior to the planned surgical procedure and with their permission written study information was sent by mail. Informed consent was retrieved by a trained research professional 1 day before surgery. Inclusion took place between August 2014 and July 2018.

Data Collection and Study Procedures

Patient characteristics were collected from routine preoperative anesthesia assessment and consisted of medical history, current drug use, laboratory tests and echocardiography results. Surgical characteristics and study data were prospectively collected and started at time of hospital admission. Anesthesia and intensive care unit (ICU) management were conducted following local standard operating procedures for cardiac surgery. For CPB, non-pulsatile perfusion was used with a flow of 2.0 to 2.4 l/min/m² and unfractionated heparin was used to target the kaolin activated clotting time (ACT) >400 s. After aortic cross-clamping, cardiac arrest was initiated using a cold crystalloid cardioplegia solution (St. Thomas cardioplegia, Pharmacy 'Haagse Ziekenhuizen', The Hague, Netherlands) while CPB provides organ perfusion. During the phase of HCA with a core temperature of 25 °C, brain tissue was preserved using bilateral antegrade selective cerebral perfusion. Patients were weaned from CPB after rewarming (temperature >35.5 °C). Heparin was reversed with protamine sulfate (0.75 mg per 100 U of heparin) and tranexamic acid was administered to each patient.

Blood Product Transfusion Algorithm

Blood product transfusion was performed according to a local transfusion protocol. The trigger for red blood cell (RBC) transfusion was a hematocrit (Ht) <0.20 during CPB or <0.25 after CPB; a hemoglobin (Hb) <4.4 mmol/l (7.1 g/dl) during ICU stay. Plasma transfusion was based on intraoperative blood loss (ie, the number of transfused cell saver units or clinical signs of coagulopathy after protamine administration) or ongoing blood loss and an international normalized ratio of prothrombin time (INR) >1.5 after ICU arrival. Platelet transfusion depended on clinical signs of coagulopathy and/or low platelet count (PC) <100×10^9/l.

Blood Sampling and Coagulation Tests

Blood samples were collected from an arterial line at five perioperative time points: at baseline after induction of anesthesia (T1), after CPB (T2), after administration of study medication (T3), at ICU arrival (T4) and 24 hours postoperative (T5). Whole blood was sampled in K_2EDTA and 3.2% sodium citrate tubes for conventional blood tests (T1,2,4; Hb, Ht and

PC) and Fibrinogen (T1-5; Clauss assay, STA-R Evolution Analyzer, Diagnostica STAGO, France), and citrate plasma samples (T1,4) were stored at $-80\,°C$. Viscoelastic point-of-care (POC) testing was performed on a TEG 5000-analyzer (Haemonetics Corp., USA) at T1-T3 by a research professional within 5 minutes after sampling. Viscoelastic POC tests included: kaolin initiated clotting time (R; min), time from initial clot formation until maximum firmness (alpha angle (AA); degrees), clot strength (MA; mm) and functional fibrinogen (FF). Thrombin generation measurements at baseline (T1) and ICU arrival (T4) were performed in stored samples in batch. The citrate plasma samples were thawed for 5 minutes at $37\,°C$, gently mixed and centrifuged for 5 minutes at 13 400 rpm. TGA's were performed on the ST Genesia analyzer (Stago, Asnières-sur-Seine, France) using the BleedScreen application.[12] All samples of each patient were analyzed in the same experimental run, including the parameters for the endogenous thrombin potential (ETP; nM min), the initiation phase of clotting (lag time; min), the maximal amount of thrombin formed (peak height; nM), and the time to peak (min).

Intervention

Study medication was prepared by a trial pharmacist after aortic arch reconstruction during CPB rewarming. FC was dissolved in a blinded infusion bag with sterile water (1 g per 50 ml). Fibrinogen dose was based on patient weight, using the following dosing regimen: 4 g/200 ml for weight <70 kg; 6 g/300 ml for weight 70-90 kg; 8 g/400 ml for weight >90 kg.[12] Placebo was a weight adjusted equivalent volume of sodium chloride 0.9% (Freeflex, Fresenius Medical Care Nederland B.V.). All study medication was administered through an 18-gauche peripheral colored intravenous line.

Study medication was only administered if clinically relevant bleeding occurred after CPB and when completion of surgical hemostasis for focal bleeding was accomplished by the surgeon. The 5-minute intraoperative bleeding mass was determined by weighing dry surgical gauzes, applying them into the surgical field for 5 minute with no touch or irrigation and weighing them again. Blood volume weight between 60 and 250 g was classified as clinically relevant coagulopathic bleeding.[9] After administration of study medication, 5-minute bleeding mass was measured again.

Outcomes

The primary outcome parameter was number of perioperative transfused allogeneic blood products within 24 hours (h) after surgery. Secondary outcome parameters were blood loss after surgery (chest tube drainage volume 24 after surgery), reoperation (30 days) and postoperative mortality (30 days). Tertiary outcome parameters included the course of coagulation parameters including plasma fibrinogen, thromboelastography and thrombin generation assays.

Randomization and Blinding

Before surgery patients were randomly allocated by a clinical pharmacist to receive FC or placebo using block randomization (8 patients per block). Blinding of the investigators and surgical team was ensured by maintaining equivalent volumes of study medication in an infusion bag wrapped in aluminum foil.

Sample Size

Based on historical transfusion data in patients with aortic replacement surgery from our institution (median number of 24 hours blood transfusions 9 ± 7) we hypothesized that two groups of 39 patients were required to demonstrate a 50% reduction of blood transfusion products in 60% of patients (power 90%, with an α of 0.05).
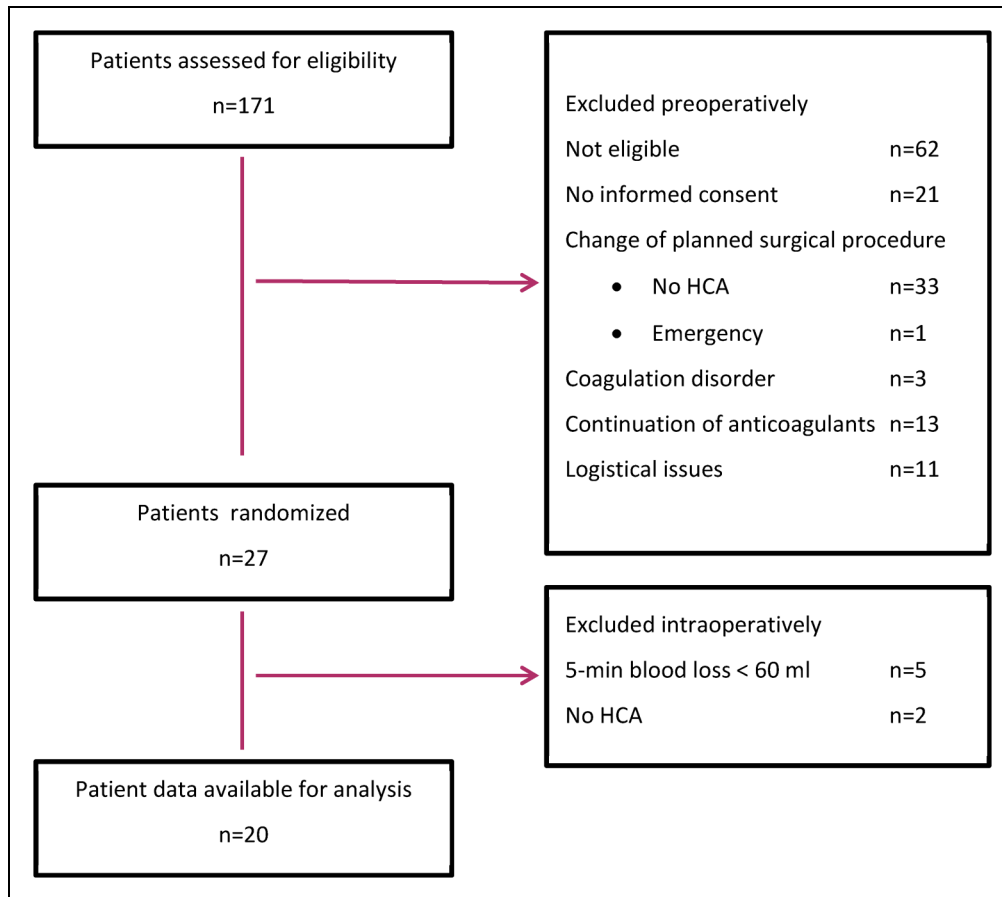
Statistical Analysis

Descriptive statistics were calculated for all parameters as appropriate. Normality was tested using visual inspection of histograms. To compare categorical variables and continuous variables between groups Pearson Chi-squared test, Fisher's exact test, Student's t-test or Mann–Whitney U test were performed as appropriate. For estimating a difference in the primary outcome parameter, Mann–Whitney U test was conducted on the number of transfused blood products according to study medication. Exploratory analysis was performed for secondary endpoints. The tertiary outcome TGA parameters at ICU arrival compared to baseline were studied according to study medication using Mann–Whitney U test. Missing data were assumed missing completely at random and were excluded from analysis. No adjustment for multiple statistical comparisons was used. All statistical analyses were performed in IBM SPSS 24.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Study Population

Between August 2014 and July 2018, 171 patients with a thoracic aneurysm were screened for study participation and 73 patients were considered eligible and received study information (Figure 1). Twenty-seven patients provided informed consent and were randomized to receive FC or placebo. During surgery 2 patients were excluded because aortic replacement surgery was performed without HCA and 5 patients had insufficient intraoperative bleeding. On November 2014, the data and safety monitoring board was consulted early for a serious adverse event (one patient died of mesenteric ischemia) and concluded that the study should be continued based on the results of an interim analysis. The recruitment of study patients was terminated in December 2018 due to a low inclusion rate.

Twenty patients were treated with FC ($N = 10$) or placebo ($N = 10$). Mean age was 63 (± 12) years, mean weight was 87

Figure 1. Patient flow diagram. HCA, hypothermic circulatory arrest.

(±20) kg and 6 (30%) patients were female. Baseline characteristics are listed in Table 1. Fibrinogen concentration at the end of CPB and before study medication was 1.5 [1.4-1.7] g/l for the fibrinogen group and 1.6 [1.4-2.1] g/l for the control group. The mean decrease in plasma fibrinogen concentration compared to baseline was 47% (±7) and 18 (90%) patients had a fibrinogen concentration <2 g/l. After FC administration the plasma concentration increased from 1.5 [1.4-1.7] g/l to 3.1 [2.8-3.3] g/l (P=0.005). At time of ICU arrival fibrinogen concentration was 3.0 [2.6-3.3] g/l in the fibrinogen group and 1.8 [1.5-2.2] g/l in the control group (P=0.001). The difference in plasma fibrinogen concentration was no longer present at 24 hours after surgery (4.4 [3.4-4.7] g/l for the fibrinogen group and 3.6 [3.2-4.4] g/l for the control group, P=0.267).

Blood Transfusion and Blood Loss

Five (50%) patients in the fibrinogen group and 2 (20.0%) patients in the placebo group had at least one perioperative blood transfusion (P=0.196). Number and types of perioperative blood transfusions are presented in Table 2. Intraoperative bleeding after CPB was not different between both groups (5-minute bleeding mass 131 [90-188] g for the fibrinogen group and 142 [79-158] g for the control group,

P=0.821). After study medication 5-minute bleeding mass was reduced by 52% [33-67] in patients that received FC compared to 32% [16-80] in patients treated with placebo (P=0.705). Median postoperative blood loss was 490 ml [393-635]. Postoperative blood loss was 450 ml [300-655] for the fibrinogen group and 510 ml [415-650] for the control group (P=0.405) (Figure 2).

One patient in the fibrinogen group had a reoperation because of mesenteric arterial occlusion. In both groups one patient died during hospital stay, cause of death was mesenteric ischemia in the fibrinogen patient and sepsis in the placebo patient. One patient in the placebo group suffered from a non-fatal stroke.

Point-of-Care Coagulation Assays

Thromboelastography test results are presented in Figure 3. Values at baseline, post-CPB and after study medication were similar between groups. A reduction in clot strength between baseline and post-CPB (ΔTEG-MA) was related to intraoperative blood loss ($r = -0.468$ for 5-minute bleeding mass, P=0.043). After study, medication clot strength and time until maximum firmness improved significantly in the FC group but not in the control group (Figure 3). Test

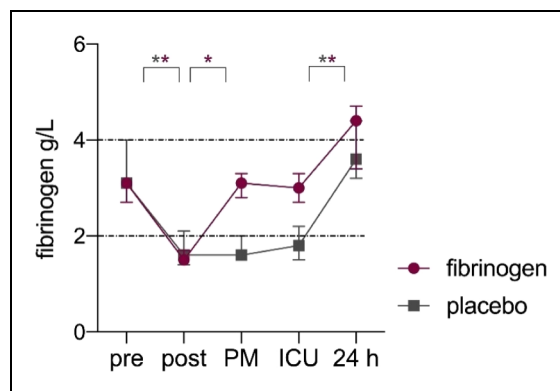**Table 1.** Baseline and Clinical Characteristics.

Demographics	Fibrinogen $n = 10$	Placebo $n = 10$	Missing
Age, median [IQR], years	67 [55-74]	64 [50-67]	0
Female, No. (%)	4 (40)	2 (20)	0
Weight, mean (SD), kg	86 (24)	89 (15)	0
EuroSCORE, median [IQR]	7.5 [5-10]	6.5 [5-8]	0
Diabetes, No. (%)	0 (0)	0 (0)	0
Hypertension, No. (%)	6 (60)	6 (60)	0
LVEF %, No. (%)			0
<30	0	0	
30-50	3 (30)	3 (30)	
>50	7 (30)	7 (70)	
Aortic valve surgery, No. (%)	4 (40)	8 (80)	0
CPB time, median [IQR], minutes	198 [174-225]	222 [195-259]	0
Cerebral perfusion time, median [IQR], minutes	30 [26-47]	33 [27-57]	0
Transfusion autologous blood, median [IQR], ml	833 [600–1700]	1100 [550-1300]	1
5-Minute bleeding mass before SM, median [IQR], ml	131 [90-188]	142 [79-158]	0
5-Minute bleeding mass after SM, median [IQR], ml	65 [39-104]	61 [40-108]	0
Laboratory			
Hb, mmol/l	8.0 [7.3-8.7]	7.8 [6.7-8.9]	0
Ht, %	0.38 [0.35-0.40]	0.37 [0.33-0.41]	0
Platelet count, $\times 10^9$/l	191 [163-212]	208 [161-249]	0
Fibrinogen, g/l	3.1 [2.7-3.2]	3.1 [2.7-4.0]	0
Aptt, s	34.9 [32.3-36.9]	34.4 [31.9-38.7]	3
Thromboelastography			
TEG-MA, mm	67.4 [65.2-69.8]	68.5 [64.6-72.7]	0
TEG-R, minutes	7.2 [4.7-8.9]	6.9 [3.9-8.6]	0
TEG-AA, °	62.1 [59.7-68.3]	65.8 [63.4-71.8]	0
FF-MA, mm	26.7 [22.5-40.6]	30.9 [27.5-38.7]	1
Thrombin generation assay			2[a]
ETP, nM minutes	842 [720-1122]	869 [636-1140]	
Lag time, minutes	3.6 [3.3-4.1]	4.1 [3.6-5.0]	
Time to peak, minutes	7.3 [6.7-8.1]	7.6 [6.4-8.7]	
Peak height, nM	118 [78-144]	110 [80-178]	

CPB, cardiopulmonary bypass; SM, study medication; TEG, thromboelastography; R, kaolin initiated clotting time; AA, angle from initial clot formation until maximum firmness; MA, maximum clot strength; FF, functional fibrinogen; ETP, endogenous thrombin potential.
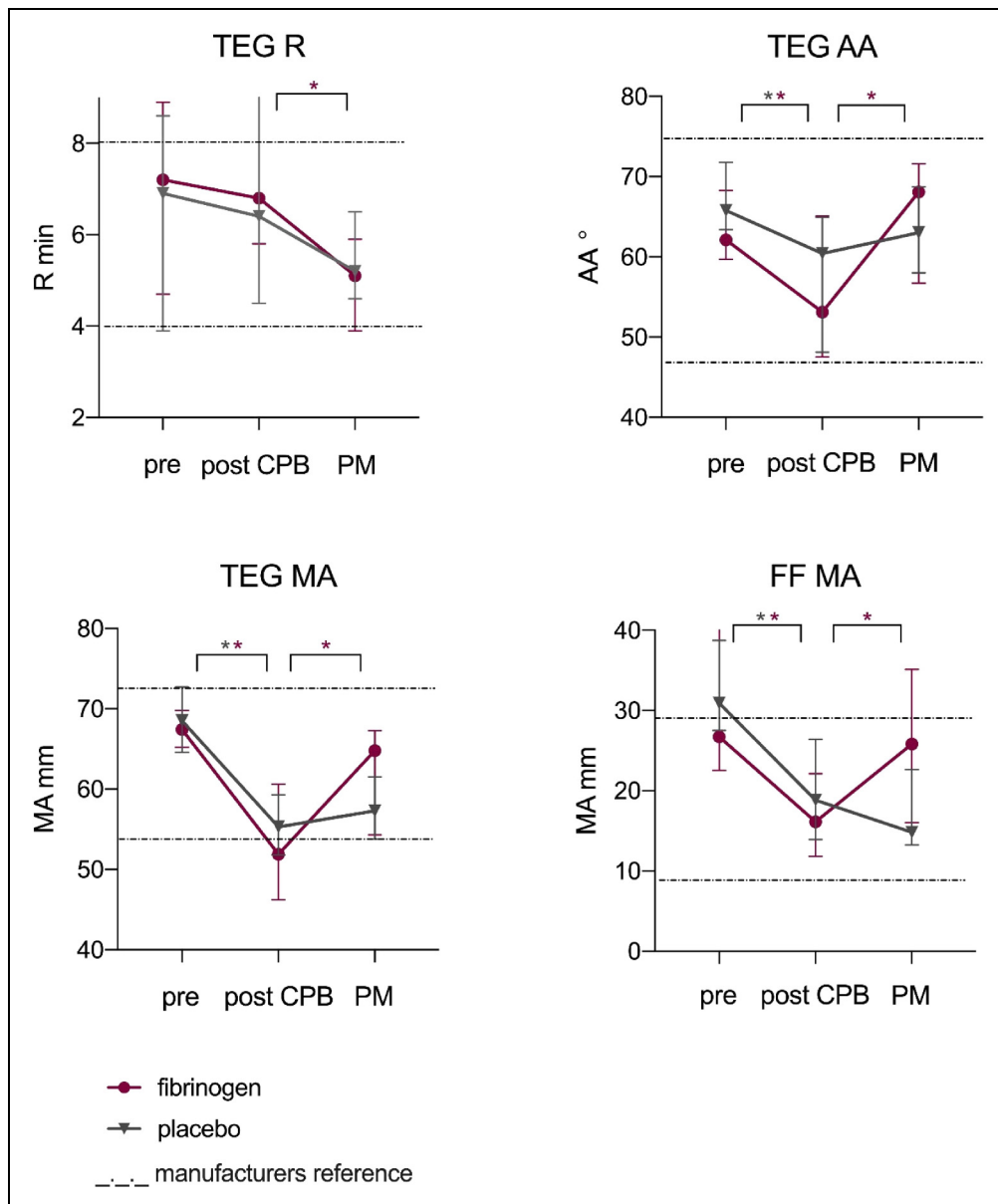[a]For TGA the data of 2 patients (1 of both groups) were missing.

Table 2. Perioperative Blood Transfusions.

	Fibrinogen	Placebo	P	Missing
Intraoperative blood transfusions, units (range)				
Red Blood Cells	3 (1-2)	1 (1)	0.503	0
Plasma	1 (1)	2 (2)	0.942	0
Platelets	2 (1)	1 (1)	0.542	0
Postoperative blood transfusions (24 hours), units (range)				
Red Blood Cells	1 (1)	0	0.317	0
Plasma	2 (2)	0	0.317	0
Platelets	1 (1)	0	0.317	0

Figure 2. Perioperative fibrinogen concentrations in fibrinogen and placebo group. Median values and error bars, IQR. Dashed lines indicate reference lines. Pre (T1), baseline; post (T2), post-CPB; PM (T3), post-study medication. *P<0.05. Ranges of fibrinogen levels (g/l) were T1, 2.3-5.0 and T2, 1.0-2.9; after fibrinogen T3, 2.4-3.5; T4, 2.3-3.5; T5, 3.1-5.3; after placebo T3, 1.1-2.7; T4, 1.0-2.9; T5, 2.4-4.7.

results for clot strength and FF returned to baseline in the FC group (−7% difference compared to baseline for TEG-MA (P=0.203) and −15% difference for FF-MA (P=0.241)) but

Figure 3. Perioperative thromboelastography. Values at baseline (pre), post-CPB and after study medication (PM). Data markers indicate median and error bars, IQR. Dashed lines indicate manufacturers reference values. *P<0.05.

Table 3. Postoperative Thrombin Generation.

	ICU			Median difference; ICU − baseline		
	FC+	FC−	P*	FC+	FC−	P**
ETP, nM minutes	863 [452-1142]	452 [201-545]	0.019	−100 [−365 to −72]	−562 [−625 to −343]	0.014
Lag time, minutes	5.1 [3.7-5.9]	5.8 [4.9-9.7]	0.077	0.9 [−0.1 to 1.8]	2.4 [0.8-3.9]	0.040
Time to peak, minutes	8.5 [6.9-10.3]	8.9 [8.1-14.7]	0.113	0.1 [−0.6 to 2.1]	2.5 [0.7-5.6]	0.031
Peak height, nM	100 [49-133]	54 [21-65]	0.040	−27 [−49 to −23]	−83 [−113 to −44]	0.014

Comparison between groups at ICU arrival (P*). Comparison of median difference (ICU arrival values minus baseline values) between groups in TGA (P**). P<0.05. FC, fibrinogen concentrate; ETP, endogenous thrombin potential, expressed in nM minute.

did not in the control group (−16% difference compared to baseline for TEG-MA (P=0.005) and −53% difference for FF-MA (P=0.008)).

The thrombin generation in stored samples at baseline was similar (Table 1) but at ICU arrival the primary parameters of interest, ETP and peak height, were significantly higher in the

FC group (ETP 863 vs 452 nM min after placebo, P=0.019 and peak height 100 vs 54 nM after placebo, P=0.014). As thrombin regulation capacity varies widely between individuals, we assessed the change in thrombin generation between baseline and ICU arrival. We observed a more preserved procoagulant state in patients with FC as the reduction of thrombin generation was smaller, displayed by a lower decline in ETP (−9% vs −59%, P=0.014) and peak height (−18% vs −66%, P=0.014), and less increased time to peak (1% vs 39%, P=0.031) and, lag time (26% vs 63% in placebo, P=0.040) at ICU arrival (Table 3).

Comment

This study aimed to determine the effect of intraoperative treatment with FC on perioperative blood product transfusion in patients with elective aortic arch replacement surgery using HCA. A difference in number of blood transfusions after treatment with FC could not be demonstrated because the recruitment of study patients was unsatisfactory and the sample size was insufficient to answer the primary research question. Patients treated with FC showed a more preserved procoagulant state including a post-CPB improvement in fibrinogen concentration, clot strength and time until maximum clot firmness, and a smaller reduction of thrombin generation at ICU arrival, compared to patients treated with placebo.

Prior studies on the effect of treatment with FC to reduce blood transfusions in cardiac surgery patients have shown conflicting results.[9–11,13–15] A single-center randomized trial published in 2013, demonstrated that intraoperative treatment with FC resulted in an 85% reduction of blood transfusions in patients undergoing aortic replacement surgery.[9] Total avoidance of transfusion was achieved in almost half of the FC patients compared to none of the placebo patients. However, the number of blood transfusions in the control group was very high (median 13 units vs 2 units in the FC group) and the favorable effect of FC treatment on blood transfusion after aortic replacement surgery could not be confirmed in a follow-up multicenter study in 2016 with a similar design.[10] In that study, the number of transfusions in the placebo group declined to a median of 3 units [0-7] and was even lower than the number of transfusions in the FC group (median 5 units [2-11]). A clear explanation for the higher transfusion rate in the FC group was not found, but could have been the result of poor protocol adherence.[16] The large decline in perioperative blood transfusions over time in patients undergoing aortic replacement surgery, irrespective of FC treatment, was also witnessed in our institution. The historical transfusion data we used for sample size analysis in 2014, showed a much higher number of transfusions than the control group of our randomized trial (median 9 ± 7 vs median 0 ± 0). Therefore, it seems unlikely that the sample size would have been sufficient to demonstrate a significant difference in transfusions between both groups, also if patient recruitment had not been prematurely ended. The implementation of a patient blood management program in 2015 that consisted of lower transfusion thresholds, an intraoperative POC transfusion algorithm, modified surgical and CPB techniques to reduce blood loss and limit intraoperative anemia could explain the overall reduction of transfusions over time in patients undergoing aortic replacement surgery in our institution.

We found that post-CPB treatment with FC resulted in an improvement of clot strength and time until maximum clot firmness compared to placebo. This finding is relevant as a reduction in clot strength between baseline and post-CPB was correlated to intraoperative blood loss. In surgical patients, viscoelastic coagulation assays are used for the early diagnosis of coagulation disorders, to guide transfusion management and consequently reduce postoperative bleeding and blood product consumption.[17–19] In cardiac surgery patients viscoelastic monitoring of fibrinogen function showed a better clinical performance than routine coagulation tests as a standardized, more reliable and valid laboratory tool for monitoring of the fibrinogen contribution to the clot formation.[3] Clot strength was found to be the best viscoelastic predictor of postoperative blood loss, while none of the routine coagulation tests showed any correlation with postoperative bleeding.[19,20]

Fibrinogen plays a key role in hemostasis and a negative association exists between plasma fibrinogen levels and blood loss after cardiac surgery.[8,21–23] Studies have shown that patients with normal or elevated fibrinogen levels experience fewer bleeding complications than patients with low fibrinogen levels.[23,24] Post-CPB fibrin formation is significantly more deteriorated than the platelet component of whole blood clot strength, suggesting that initial management of coagulopathy following cardiac surgery should focus on improving fibrin formation.[25] While the critical level of plasma fibrinogen, in relation to perioperative blood loss, remains subject of debate, there are experimental and clinical data describing that fibrinogen improves clot strength dose dependently.[26,27] In our study the median post-CPB fibrinogen concentration was below the threshold of 2.0 g/l in 90% of patients, but most patients had little blood loss and a beneficial effect of FC treatment to reduce the number of blood transfusion products could not be established.

In summary, our results provide interesting insights in coagulopathy after cardiovascular surgery using HCA. We found that intraoperative FC treatment efficiently restored fibrinogen levels and clot strength to preoperative values with a more efficiently preserved postoperative thrombin generation. Considering the complexity of coagulopathy after cardiac surgery, a combination of viscoelastic and thrombin generation assays may improve our understanding of the dynamics of global hemostasis. Our study was not equipped to elucidate the association of thrombin generation with postoperative coagulopathy or bleeding, but the more preserved thrombin generation in patients with FC may be considered hypothesis generating. Assays that are amendable to POC application are upcoming, and future research is needed to confirm whether thrombin generation testing has the potential to reduce bleeding complications and what could be the optimal treatment of decreased thrombin generation in the postoperative phase.

Limitations

The major drawback is the low power of the study. Our trial was prematurely ended due to low inclusion rates. More than expected, patients were not eligible for study participation due to use of anticoagulants, a history of thrombosis and we overestimated the willingness of patients to participate in a clinical intervention study. The main reasons to refrain from study participation were anxiety for the surgical procedure or fear for adverse outcome. We aimed to include patients at high risk for postoperative bleeding based on type of surgery, use of HCA and historical data. However, overall blood loss was low. This may be the result of a Hawthorne effect. Finally, different aspects of a patient blood management program could have influenced blood loss in favor of patient outcome.

Conclusion

This study demonstrated that low fibrinogen levels are common after elective aortic replacement surgery using HCA. Treatment with FC effectively restored fibrinogen levels and improved clot strength including a better preserved postoperative thrombin generation capacity, but a reduction in transfusion or blood loss could not be demonstrated.

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