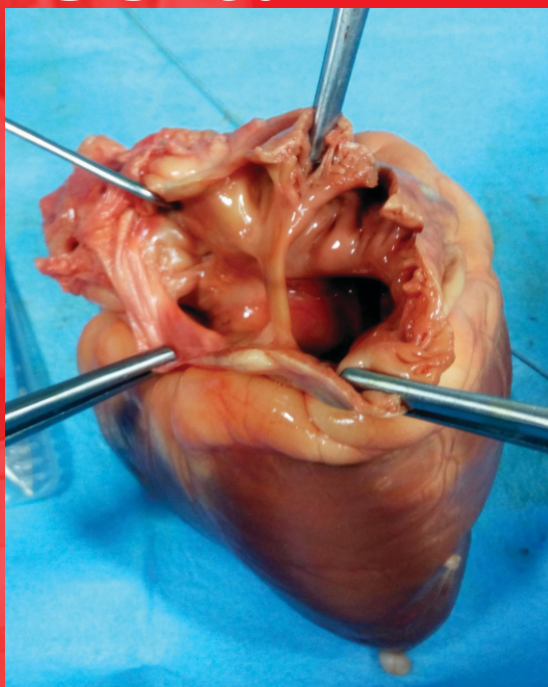




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A Low-dose Human Fibrinogen is not Effective in Decreasing Postoperative Bleeding and Transfusion Requirements during Cardiac Surgery in Case of Concomitant Clinical Bleeding and Low FIBTEM Values: A Retrospective Matched Study

Abstract

Background: Studies evaluating the hemostatic effects of fibrinogen administration in cardiac surgery are not conclusive. **Aims:** We investigated whether the use of a low-dose human fibrinogen in case of clinical bleeding after protamine administration and concomitant low FIBTEM values is effective in reducing postoperative bleeding. Secondary end-point was to investigate the consumption of allogeneic blood products. **Setting and Design:** This was a retrospective matched study conducted at university hospital. **Materials and Methods:** Among 2257 patients undergoing surgery with cardiopulmonary (CPB) bypass, 73 patients received a median dose of 1 g human fibrinogen (ROTEM-Fibri group). This group was matched with 73 patients who had not received human fibrinogen (control group) among 390 patients having undergone surgery at the moment FIBTEM analysis was unavailable. **Statistical Analysis:** Matching was performed for the type and the presence of redo surgery. McNemar and Wilcoxon paired tests were used to respectively compare the categorical and quantitative variables. **Results:** The CPB bypass time was significantly higher in the ROTEM-Fibri group ($P = 0.006$). This group showed significantly higher bleeding in the first 12 and 24 h postoperatively ($P < 0.001$) and required significantly more transfusion of blood products ($P < 0.001$) and surgical revision ($P = 0.007$) when compared with the control group. There was no significant difference in the number of thromboembolic complications. **Conclusions:** These results show that the administration of 1 g of fibrinogen based on low-FIBTEM values and clinical bleeding after protamine administration does not stop bleeding and the need for transfusion of allogeneic blood products.

Keywords: Bleeding, cardiopulmonary bypass, human fibrinogen, point-of-care test ROTEM®, transfusion

Introduction

Despite advances in surgical and cardiopulmonary (CPB) techniques, patients undergoing cardiac surgery with CPB remain at high risk of intraoperative and postoperative bleeding.^[1-3] Moreover, an increasing number of patients take various antiplatelet or anticoagulant therapies, putting them at high risk of perioperative bleeding.^[4-6] Our group has previously shown that circulating fibrinogen level significantly decreases after first-time on-pump versus off-pump coronary artery bypass surgery when analyzed with the Clauss method as well as with the point-of-care (POC) test, Rotational Thromboelastometry (ROTEM®).^[7] This drop in fibrinogen concentration is primarily caused by hemodilution.^[8]

Recently, numerous studies have suggested that first-line high-dose fibrinogen administration reduces postoperative bleeding^[9-12] and the need for transfusion of hemostatic factors.^[10,11,13-15]

Pasteurized human fibrinogen is currently available in 44 countries.^[16] However, in many countries, it is only reimbursed in case of congenital fibrinogen deficiency.

The aim of this study was to show that off-label use of a low dose of human fibrinogen in case of clinical bleeding after protamine administration associated with pathological fibrin-based thromboelastometry test FIBTEM, is effective in reducing bleeding after cardiac surgery with CPB. Secondary end-point was to show reduced consumption of

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allogeneic blood products in patients who had received human fibrinogen concentrate.

Materials and Methods

This was a retrospective, cohort study. The review of the patients' medical records was approved on February the 16th 2016 by Local Ethics Committee (2016/01FEV/033). The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2010. We analyzed the data of adult patients who underwent elective or emergency cardiac surgery with CPB. In our institution, off-label use of human fibrinogen is only authorized in case of clinical bleeding together with FIBTEM Maximum Clot Firmness (MCF) values of ≤ 6 mm. In exceptional cases when clinical bleeding was very important, higher cutoff values of FIBTEM MCF were accepted to administer human fibrinogen. The POC test ROTEM® has been introduced in our institution in 2008. Before its introduction, human fibrinogen was only administered when the circulating fibrinogen concentrations were lower than 100 mg/dL as measured by the Clauss method.

Between June 2012 and August 2015, a total of 2257 adult patients underwent cardiac surgery with CPB. In case clinical bleeding persisted after protamine administration, ROTEM analysis was performed together with the fibrinogen measurements based on the Clauss method. At the same moment, the POC test Multiplate analyzer® was performed as well to analyze the platelet function. Among the 2257 patients, 73 subjects received human fibrinogen because of clinical bleeding and FIBTEM MCF values ≤ 6 mm (ROTEM-Fibri group). The decision to transfuse hemostatic factors was based on the analysis of the POC tests and adapted to the clinical situation. This decision was taken by the anesthesiologist in charge of the patient.

No cryoprecipitate was administered in any study group as it is not available in our institution.

From March 2008 to November 2008, 390 patients had undergone cardiac surgery with CPB. During this period, no POC tests were available. Of these 390 patients, 73 patients (Control group) were matched with the 73 patients in the ROTEM-Fibri group.

Routine normothermic CPB at a standardized continuous nonpulsatile flow of 2, 4 L/min/m² was performed in both groups. In patients undergoing aortic arch surgery or aortic dissection, moderate hypothermia (28°C) with circulating arrest and antegrade selective cerebral perfusion was realized. CPB prime varied slightly over the different study periods. It consisted of 1000 mL Ringer Acetate Solution Plasmalyte A®, Baxter, S. A. Lessines, Belgium with a mixture of either 500 mL Ringer Acetate solution or 500 mL HES 6% 130/0,4 (Voluven® or Volulyte®, Fresenius Kabi, Belgium), together with 100 mg of heparin and 2 mL/kg of Mannitol 15%. Packed red blood cells (RBCs)

were transfused to achieve a hematocrit of $>20\%$ on CPB. Tranexamic acid was used in all patients in both groups with a maximum dose of 30 mg/kg. Half of this dose was administered at the induction of anesthesia and half was given in the CPB machine. This dose was decreased in case of chronic kidney disease. No patients received aprotinin. A cell-saver was used in all the cases. The same senior surgeons were in charge of the patients over the both study periods.

Statistical analysis

The distribution of the data was tested using Smirnov-Kolmogorov test. All data are expressed as median (Percentile 25-Percentile 75) and numbers (percentages) as appropriate. To account for differences in baseline and clinical characteristics, a one-to-one propensity score matching was realized. Matching without replacement was used. Categorical variables used for exact matching were the type of surgery and eventual redo surgery. No continuous variables were used for matching. The use of CPB time led to poor matching. A McNemar test and a Wilcoxon-paired test were used to, respectively, compare categorical and quantitative variables between the matched groups. A previous analysis of our cardiac surgical patients revealed mean postoperative bleeding of 950 ± 700 mL in the first 12 h postoperatively. We hypothesized that with the administration of human fibrinogen, the 12 h postoperative bleeding would decrease to 600 mL. To demonstrate this, at least a total number of 63 patients were required in each group with a power of 80% and a two-sided α -error at 0.05.

All *P* values were two-sided and were considered to be statistically significant if <0.05 . Statistical analysis was carried out using IBM® SPSS® Statistics Software Package version 23.

Results

Preoperative characteristics of the two matched groups and not: two-matched groups are shown in Table 1. Despite matching, the characteristics of both groups were not entirely similar. Patients in the ROTEM-Fibri group had significantly lower preoperative platelet count ($P = 0.02$). Their circulating fibrinogen levels were lower as well although this difference did not reach statistical significance ($P = 0.09$). They also showed some differences in the routine coagulation tests when compared with the control group. The intraoperative data are illustrated in Table 2. As previously mentioned, the CPB time was significantly higher in the ROTEM-Fibri group ($P = 0.006$). Matching both groups for CPB time resulted in only a very small group of patients and was as such abandoned. The perioperative transfusion data are illustrated in Table 3. Significantly, more patients in the ROTEM-Fibri group were transfused with significantly more allogeneic blood products of any kind, not taking

Table 1: Preoperative characteristics

	Control group	ROTEM-fibri group	P
Age (years)	66 (58-74)	57 (37-68)	0.001
Weight (kg)	79 (64-87)	74 (62-83)	0.05
Gender male	49 (67)	55 (75)	0.35
Shortening fraction (%)	33 (22-38)	33 (21-40)	0.30
Diabetes	11 (15)	7 (10)	0.45
Creatinine (mg/dL)	1.1 (0.9-1.5)	1.0 (0.8-1.2)	0.02
Anticoagulant/antiplatelet therapy	49 (67)	42 (58)	0.27
Anticoagulant/antiplatelet therapy stopped	8 (16)	8 (19)	0.99
Platelet count (cells, $\times 1000 \mu/L$)	216 (178-249)	192 (152-225)	0.02
Fibrinogen concentration (mg/dL)	351 (300-416)	317 (280-372)	0.09
Activated partial thromboplastin time (s)	27 (25-29)	31 (29-34)	<0.001
Prothrombin time (s)	11.2 (10.7-11.9)	12.0 (10.7-13.6)	0.02
International normalized ratio	1.04 (0.99-1.11)	1.05 (0.97-1.20)	0.89
Thrombin time (s)	19 (18-21)	15 (14-16)	<0.001

Data are expressed as median (percentile 25 to percentile 75) or *n* (%). ROTEM: Rotational thromboelastometry

Table 2: Intraoperative data

	Control group	ROTEM-fibri group	P
Type of surgery			0.35
CABG	3 (4.1)	9 (12.3)	0.15
Valve surgery (1 or more)	23 (31.5)	22 (30.1)	0.99
CABG + valve surgery (1 or more)	17 (23.6)	6 (8.2)	0.03
Thoracic aorta/valve preserving aortic reimplantation	23 (31.5)	24 (32.9)	0.99
Transplantation/ventricular assist device	7 (9.6)	12 (16.4)	0.33
Emergency surgery	15 (21)	20 (27)	0.41
Redo surgery	28 (38)	28 (38)	1.00
Cardiopulmonary bypass time (min)	105 (80-160)	146 (119-186)	0.006
Aortic cross-clamp time (min)	74 (54-113)	84 (57-124)	0.62
Cell-saver (mL)	800 (620-988)	854 (620-1385)	0.64

Data are expressed as median (percentile 25 to percentile 75) or *n* (%). CABG: Coronary artery bypass grafting, ROTEM: Rotational thromboelastometry

into account the administered fibrinogen ($P < 0.001$). The administration of human fibrinogen did not stop bleeding as shown in Table 3. In the ROTEM-Fibri group despite the administered fibrinogen, 47 (78%), 24 (37%), and 39 (57%) of patients were transfused with, respectively, RBC, fresh frozen plasma (FFP), and platelet concentrates. Patients under Vitamin K antagonists and coming for emergency surgery received prothrombin complex concentrate. No patients received human antithrombin and prothrombin complex concentrate in the postoperative period. The blood analysis results and postoperative data are shown in Table 4. The circulating plasma fibrinogen levels at the time POC tests were performed was 114

(113–135) mg/dL. The FIBTEM MCF values before and after fibrinogen administration were, respectively, 6 (5–7) mm and 12 (11–14) mm. As mentioned earlier, the POC test Multiplate analyzer® was used as well to analyze the platelet function at the moment the ROTEM analysis was performed. The results of this test are illustrated in Table 4. At arrival in the intensive care unit (ICU), there was no statistically significant difference between the circulating fibrinogen levels and the platelet count of both groups. Patients in the ROTEM-Fibri group showed significantly higher postoperative bleeding in the first 12 h as well as 24 h after arrival in the ICU ($P < 0.001$). When compared with the control group, significantly more patients in the ROTEM-Fibri group returned to the operating and not theatre for tamponade or surgical hemostatic revision ($P = 0.007$). The percentage of patients showing hemostatic problems or combined surgical and hemostatic problems was higher in the ROTEM-Fibri group as shown in Table 4. Some of the patients coming for heart transplantation or ventricular assist device procedures required an extracorporeal membrane oxygenator. This was the case in 3 patients in the ROTEM-Fibri group and 1 patient in the control group.

Discussion

The results of this retrospective study show that the administration of a low dose of human fibrinogen in bleeding cardiac patients presenting with low FIBTEM MCF values does not stop bleeding and the need for allogeneic blood product transfusion.

Several randomized trials in complex cardiac surgery have shown promising results in terms of bleeding and transfusion of allogeneic blood products when human fibrinogen concentrate is administered at high doses.^[9,13,14] However, recently, other studies have failed to show a positive effect of human fibrinogen concentrate in cardiac surgery patients.^[17-19] Table 5 summarizes the design and the results of the 4 recent double-blinded, placebo-controlled

Table 3: Perioperative transfusion data

	Control group	ROTEM-fibri group	P
Number of patients transfused with any product*	44 (60)	73 (100)	<0.001
Number of patients transfused RBC	37 (51)	60 (82)	<0.001
		Before fibrinogen: 41 (68)	
		After fibrinogen: 47 (78)	
Number of patients transfused FFP	27 (37)	65 (89)	<0.001
		Before fibrinogen: 53 (82)	
		After fibrinogen: 24 (37)	
Number of patients transfused platelets concentrate	32 (44)	68 (93)	<0.001
		Before fibrinogen: 61 (90)	
		After fibrinogen: 39 (57)	
Packed RBC - number of units	1 (0-2)	4 (2-9)	<0.001
		Before fibrinogen: 1 (0-4)	
		After fibrinogen: 2 (0-5)	
FFP - number of units	0 (0-3)	5 (3-9)	<0.001
		Before fibrinogen: 3 (1-4)	
		After fibrinogen: 2 (0-6)	
Units platelets concentrate	0 (0-7)	21 (14-35)	<0.001
		Before fibrinogen: 14 (7-14)	
		After fibrinogen: 7 (0-21)	
Dose fibrinogen per kg (mg/kg)	0	17 (13-26)	
Dose fibrinogen (g)	0 (0-0)	1 (1-2)	
Dose fibrinogen (g): Minimum-maximum		1-2	

*Any product not taking into account the administered human fibrinogen. Data are expressed as median (percentile 25 to percentile 75) or *n* (%). RBC: Red blood cell, FFP: Fresh frozen plasma, ROTEM: Rotational thromboelastometry

randomized, trials in cardiac surgery that have evaluated the efficacy of human fibrinogen administration.^[14,17-19]

A major limitation of our study is that we matched a subgroup of patients showing a high bleeding rate with an average population of patients undergoing cardiac surgery. While the design of our study very much differs when compared with the available positive^[9-15] and negative^[17-19] trials, it raises several important questions and highlights the need for optimal study designs in the future to show the risk-benefit ratio of human fibrinogen use in cardiac surgery.

First, in this study, patients in the ROTEM-Fibri group had significantly lower preoperative platelet counts compared with the control group. They also showed somehow lower preoperative circulating fibrinogen concentrations although this difference did not reach statistical significance. In a prospective, observational study on 1954 cardiac surgical patients, the preoperative fibrinogen concentration was inversely proportional to the prevalence of excessive bleeding in multivariate logistic regression analysis.^[20] Other studies have found the importance of high preoperative fibrinogen plasma concentration on postoperative bleeding in cardiac surgery.^[21,22] The guidelines of the European Society of Anaesthesiology consider the possibility of fibrinogen supplementation when levels are below 150–200 mg/dL or POC tests indicate signs of functional fibrinogen deficit.^[23]

On the other hand, low preoperative platelet count has been shown to be among predictors of blood loss after cardiac surgery.^[24] Ranucci *et al.* found that preoperative fibrinogen plasma values below 250 mg/dL could be considered as a safe cutoff value for possible preoperative fibrinogen supplementation.^[25] Otherwise recent studies suggest the usefulness of fibrinogen administration in case of thrombocytopenia and/or platelet dysfunction^[26,27] and have shown that functional fibrinogen makes a stronger contribution to clot firmness than platelets.^[28,29] Many cardiac surgery patients take various antiplatelet treatments and often present with thrombocytopenia as was the case in our ROTEM-Fibri group. Whether prophylactic fibrinogen administration should preferentially be performed in case of isolated hypofibrinogenemia, isolated thrombocytopenia or rather the association of both is an important issue to consider when conducting future trials. In this regard, the cutoff preoperative fibrinogen and platelet concentrations putting the patients at risk of bleeding in cardiac surgery should be analyzed to identify the subgroup of patients that will mostly benefit from fibrinogen administration. The usefulness of prophylactic fibrinogen administration needs also to be studied when other coagulation tests are not entirely within normal range as was the case in the patients in the ROTEM-Fibri group.

Second, in our study, the circulating plasma fibrinogen concentrations were considerably low at the time the

Table 4: The blood analysis results and postoperative data

	Control group	ROTEM-fibri group	P
Fibrinogen concentration before fibrinogen use* (mg/dL)		114 (103-135)	
Fibrinogen concentration at ICU arrival (mg/dL)	180 (150-221)	202 (132-224)	0.67
FIBTEM MCF before fibrinogen use (mm)		6 (5-7)	
FIBTEM MCF after fibrinogen use (mm)		12 (11-14)	
Multiplate test before fibrinogen use*			
AUC ADP		289 (153-438)	
AUC ASPI		293 (154-539)	
AUC TRAP		513 (345-766)	
Platelet count (cells, $\times 1000/\mu\text{L}$) at ICU arrival	113 (94-136)	125 (101-145)	0.19
Activated partial thromboplastin time (s) at ICU arrival	36 (30-40)	35 (33-42)	0.14
Prothrombin time (s) at ICU arrival	13.1 (12.2-13.8)	14.8 (13.9-16.3)	<0.001
International normalized ratio at ICU arrival	1.23 (1.14-1.30)	1.33 (1.24-1.45)	<0.001
Thrombin time (s) at ICU arrival	21 (19-29)	20 (18-25)	0.15
Bleeding first 12 h (mL)	540 (380-1000)	1200 (630-1710)	<0.001
Bleeding first 24 h (mL)	800 (510-1200)	1600 (970-2380)	<0.001
Surgical revision	8 (11)	22 (30)	0.007
Surgical reason	7 (87)	4 (18)	
Hemostatic problems	0	7 (32)	
Both	1 (13)	11 (50)	
Thromboembolic complications	3 (4)	1 (1)	0.63

*At this time ROTEM was performed. Data are expressed as median (percentile 25 to percentile 75) or *n* (%). MCF: Maximum clot firmness, ICU: Intensive Care Unit, AUC ADP: Area under curve adenosine diphosphate test (normal range: 607-963), AUC ASPI: Area under curve arachidonic acid test (normal range: 505-1086), AUC TRAP: Area under curve thrombin receptor-activating peptide (normal range: 868-1473), ROTEM: Rotational thromboelastometry

Table 5: Summary of the available double-blinded, placebo-controlled randomized trials in cardiac surgery evaluating the efficacy of human fibrinogen administration

	Ranucci <i>et al.</i> ^[14]	Rahe-Meyer <i>et al.</i> ^[17]	Bilecen <i>et al.</i> ^[18]	Jeppsson <i>et al.</i> ^[19]
Type of surgery	Planned complex cardiac surgery with expected CPB time of ≥ 90 min	Elective aortic surgery $\pm$ other cardiac procedures	Elective high-risk surgery	Elective CABG
Number of patients analyzed for primary endpoint	Placebo (<i>n</i> =58) Fibrinogen (<i>n</i> =58)	Placebo (<i>n</i> =74) Fibrinogen (<i>n</i> =78)	Placebo (<i>n</i> =57) Fibrinogen (<i>n</i> =58)	Placebo (<i>n</i> =24) Fibrinogen (<i>n</i> =24)
Primary endpoint	Avoidance of any allogeneic blood product usage	Number of units of allogeneic blood products within 24 h of study medication administration	Intraoperative blood loss (mL) between study medication infusion and closure of chest	Mediastinal drain loss during the first 12 h
Inclusion criteria based on blood tests or blood loss	No	Based on the first 5-min bleeding mass of 60-250 g	Bleeding volumes between 60-250 mL and plasma fibrinogen level of < 2.5 g/L at the end of CPB	If preoperative plasma fibrinogen level ≤ 3.8 g/L
Timing of study medication administration	After protamine administration	After protamine administration and surgical hemostasis	After CPB completion	After induction of anesthesia but before skin incision
Dose fibrinogen administered	Median dose of 4 g (IQR: 3-6)	Mean dose of 6.29 ± 1.97 g	Mean dose of 3.1 (95% CI: 2.7-3.5) g	2 g
Dose fibrinogen administered fix or based on blood analysis	Based on FIBTEM MCF before removal of the ACC with target FIBTEM MCF of 22 mm	Based on FIBTEM MCF at the end of CPB with target FIBTEM MCF of 22 mm	Based on post-CPB fibrinogen levels measured with the Clauss method and target fibrinogen level of 2.5 g/L	Fixed amount of fibrinogen administered
Primary endpoint reached	Yes	No	No	No (necessary number of patients not included)

CPB: Cardiopulmonary bypass, CABG: Coronary artery bypass grafting, MCF: Maximum clot firmness, IQR: Inter quartile range, ACC: Aortic cross-clamp, CI: Confidence interval

clinical bleeding was important and the ROTEM® analysis revealed pathologic. Numerous studies in cardiac surgery have shown an association between low post-CPB fibrinogen levels (<200 mg/dL) and postoperative bleeding.^[30-32] The post-CPB fibrinogen levels should indicate those patients who will be at risk of bleeding. Unfortunately, in contrast with the POC tests the results are only available after 40–45 min. Moreover, the fibrinogen analysis by Clauss method does not provide any information regarding the quality of fibrin polymerization and the strength of the fibrin polymer. This has been illustrated in a previous study where patients with a fibrinogen level of 150 mg/dL or greater but impaired fibrin polymerization were at high risk of bleeding in cardiac surgery.^[33]

Third point and one of the main issues in our study is the FIBTEM MCF value that was used as a trigger for fibrinogen supplementation. In our study, this trigger was set at ≤ 6 mm. In rare cases of severe clinical bleeding, a somehow higher trigger value was accepted. When compared with the existing literature this cutoff value seems to be too low. In the study conducted by Ranucci *et al.*, both the control group and the treatment group had a median FIBTEM MCF values of 13 mm before the start of the study medication.^[14] Erdoes *et al.* showed that FIBTEM A10 ≤ 10 mm measured at the end of the CPB identified patients with a post-CPB Clauss fibrinogen level of ≤ 150 mg/dL with a sensitivity of 0.99 and identified those without a post-CPB Clauss fibrinogen ≤ 200 mg/dL with a specificity of 0.83. In this way, fibrinogen supplementation is done without delay in patients who mostly require it.^[34] Otherwise, a retrospective study on 1077 patients showed that before weaning CPB a FIBTEM A 10 of ≤ 8 mm was the optimal cutoff for diagnosis of a fibrinogen concentration of <150 mg/dL.^[35] Future studies in a large group of patients need to analyze what FIBTEM values put the patients at risk of bleeding.

A fourth point to be considered is that in our study a median dose of 1 g of human fibrinogen was administered. Substitution of higher doses was exceptionally performed in case of very low FIBTEM MCF values and high patient's weight. In other studies, much higher doses have been administered.^[9,11,14] The safety and the necessity of these very high doses can, of course be argued. In different studies, the required dose of fibrinogen has been calculated based on the patient's weight and his/her actual FIBTEM MCF values and targeting FIBTEM MCF values of 22 mm.^[10,11,13,14] In the Zero-Plasma Trial (ZEPLAST) illustrating beneficial effects of fibrinogen administration, patients in the treatment arm received fibrinogen concentrate at a median dose of 4 g (Interquartile range: 3–6).^[14] However, a subanalysis of ZEPLAST showed that the dose of fibrinogen concentrate needed would be 3 g lower than the dose used in ZEPLAST.^[36] Therefore, studies need to analyze the optimal dosing of human fibrinogen taking

into account the post-CPB fibrinogen levels and/or target FIBTEM MCF values.

The last point is the timing of fibrinogen administration. In this study, fibrinogen was only given after the protamine administration and once the clinical bleeding was no more under control despite the administration of FFP and platelet concentrate. Others have shown that first-line fibrinogen administration is efficacious in reducing postoperative bleeding^[9-11] and transfusion of allogeneic blood products.^[13,14,37] Future studies need to find the optimal timing of fibrinogen administration and analyze its efficacy in a first-line setting compared to administrations later on.

The results of this retrospective study do not support the hypothesis that a low dose of human fibrinogen administration reduces postoperative bleeding and transfusion requirements. However, patients in our ROTEM-Fibri group belonged to a very high-risk cardiac surgery group as in 27% of the patients the surgery was performed on an emergency basis. These patients were then matched with a normal population of patients undergoing surgery with CPB. To be noted patients in the Rotem-Fibri group still showed some coagulation test abnormalities after arrival in the ICU which can be due to coagulation factor deficiency and might explain the ongoing postoperative bleeding. Another major shortcoming of this study is the significantly higher CPB time in the ROTEM-Fibri group. This occurred despite the matching for the type of the surgery and an eventual redo surgery. This difference might be because patients in the ROTEM-Fibri group underwent more valve-sparing surgery as they were significantly younger compared with the control group. Native-valve sparing surgery is indeed more complex than valve replacement. Otherwise, the difference in the CPB prime with the use of starch solution in some patients might have affected the results obtained in this study. Therefore, the results of this study might have been biased.

Taken into account all these aspects, the administration of higher doses of fibrinogen on a prophylactic basis might have stopped bleeding and the need for transfusion of allogeneic blood products in our high-risk cardiac surgery patients.

Conclusions

This study shows that the administration of a low dose fibrinogen in high risk cardiac patients presenting with clinical bleeding and pathological fibrin-based thromboelastometry test FIBTEM is not efficient in stopping bleeding and the need for allogeneic blood product transfusion. Before the use of human fibrinogen becomes routine practice in cardiac surgery patients several questions need to be answered. Moreover, well-powered trials are needed to analyze the safety issues with its use. Finally, in many European countries, human fibrinogen is not reimbursed. Therefore, the cost-effectiveness of human

fibrinogen use in cardiac surgery is an important aspect to be considered.

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Conflicts of interest

There are no conflicts of interest.

References

- Feneck RO. Anaemia and cardiac surgery. *Anaesthesia* 2016;71:611-3.
- Cobain TJ, Vamvakas EC, Wells A, Titlestad K. A survey of the demographics of blood use. *Transfus Med* 2007;17:1-5.
- Despotis G, Eby C, Lublin DM. A review of transfusion risks and optimal management of perioperative bleeding with cardiac surgery. *Transfusion* 2008;48:2S-30S.
- Gielen CL, Bruggemans EF, Stijnen T, Eikenboom J, Tavilla G, Brand A, *et al.* Stopping antiplatelet medication before coronary artery bypass graft surgery: Is there an optimal timing to minimize bleeding? *Eur J Cardiothorac Surg* 2015;48:e64-70.
- Tarzia V, Bortolussi G, Buratto E, Paolini C, Dal Lin C, Rizzoli G, *et al.* Single vs. double antiplatelet therapy in acute coronary syndrome: Predictors of bleeding after coronary artery bypass grafting. *World J Cardiol* 2015;7:571-8.
- Fitchett D, Mazer CD, Eikelboom J, Verma S. Antiplatelet therapy and cardiac surgery: Review of recent evidence and clinical implications. *Can J Cardiol* 2013;29:1042-7.
- Momeni M, Carlier C, Baele P, Watremez C, Van Dyck M, Matta A, *et al.* Fibrinogen concentration significantly decreases after on-pump versus off-pump coronary artery bypass surgery: A systematic point-of-care ROTEM analysis. *J Cardiothorac Vasc Anesth* 2013;27:5-11.
- Gielen CL, Grimbergen J, Klautz RJ, Koopman J, Quax PH. Fibrinogen reduction and coagulation in cardiac surgery: An investigational study. *Blood Coagul Fibrinolysis* 2015;26:613-20.
- Rahe-Meyer N, Hanke A, Schmidt DS, Hagl C, Pichlmaier M. Fibrinogen concentrate reduces intraoperative bleeding when used as first-line hemostatic therapy during major aortic replacement surgery: Results from a randomized, placebo-controlled trial. *J Thorac Cardiovasc Surg* 2013;145:S178-85.
- Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, *et al.* Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. *J Thorac Cardiovasc Surg* 2009;138:694-702.
- Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, *et al.* Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: A pilot study. *Br J Anaesth* 2009;102:785-92.
- Karlsson M, Ternström L, Hyllner M, Baghaei F, Flinck A, Skrtic S, *et al.* Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost* 2009;102:137-44.
- Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, *et al.* Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: A randomized, placebo-controlled trial. *Anesthesiology* 2013;118:40-50.
- Ranucci M, Baryshnikova E, Crapelli GB, Rahe-Meyer N, Menicanti L, Frigiola A, *et al.* Randomized, double-blinded, placebo-controlled trial of fibrinogen concentrate supplementation after complex cardiac surgery. *J Am Heart Assoc* 2015;4:e002066.
- Solomon C, Schöchl H, Hanke A, Calatzis A, Hagl C, Tanaka K, *et al.* Haemostatic therapy in coronary artery bypass graft patients with decreased platelet function: Comparison of fibrinogen concentrate with allogeneic blood products. *Scand J Clin Lab Invest* 2012;72:121-8.
- Costa-Filho R, Hochleitner G, Wendt M, Teruya A, Spahn DR. Over 50 years of fibrinogen concentrate. *Clin Appl Thromb Hemost* 2016;22:109-14.
- Rahe-Meyer N, Levy JH, Mazer CD, Schramko A, Klein AA, Brat R, *et al.* Randomized evaluation of fibrinogen vs. placebo in complex cardiovascular surgery (REPLACE): A double-blind phase III study of haemostatic therapy. *Br J Anaesth* 2016;117:41-51.
- Bilecen S, de Groot JA, Kalkman CJ, Spanjersberg AJ, Brandon Bravo Bruinsma GJ, Moons KG, *et al.* Effect of fibrinogen concentrate on intraoperative blood loss among patients with intraoperative bleeding during high-risk cardiac surgery: A Randomized clinical trial. *JAMA* 2017;317:738-47.
- Jeppsson A, Waldén K, Roman-Emanuel C, Thimour-Bergström L, Karlsson M. Preoperative supplementation with fibrinogen concentrate in cardiac surgery: A randomized controlled study. *Br J Anaesth* 2016;116:208-14.
- Waldén K, Jeppsson A, Nasic S, Backlund E, Karlsson M. Low preoperative fibrinogen plasma concentration is associated with excessive bleeding after cardiac operations. *Ann Thorac Surg* 2014;97:1199-206.
- Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A, *et al.* Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: A prospective observational study. *Transfusion* 2008;48:2152-8.
- Blome M, Isgro F, Kiessling AH, Skuras J, Haubelt H, Hellstern P, *et al.* Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. *Thromb Haemost* 2005;93:1101-7.
- Kozek-Langenecker SA, Afshari A, Albaladejo P, Santullano CA, De Robertis E, Filipescu DC, *et al.* Management of severe perioperative bleeding: Guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2013;30:270-382.
- Wahba A, Rothe G, Lodes H, Barlage S, Schmitz G, Birnbaum DE, *et al.* Predictors of blood loss after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 1997;11:824-7.
- Ranucci M, Jeppsson A, Baryshnikova E. Pre-operative fibrinogen supplementation in cardiac surgery patients: An evaluation of different trigger values. *Acta Anaesthesiol Scand* 2015;59:427-33.
- Schenk B, Lindner AK, Treichl B, Bachler M, Hermann M, Larsen OH, *et al.* Fibrinogen supplementation *ex vivo* increases clot firmness comparable to platelet transfusion in thrombocytopenia. *Br J Anaesth* 2016;117:576-82.
- Solomon C, Schöchl H, Hanke A, Calatzis A, Hagl C, Tanaka K, *et al.* Haemostatic therapy in coronary artery bypass graft patients with decreased platelet function: Comparison of fibrinogen concentrate with allogeneic blood products. *Scand J Clin Lab Invest* 2012;72:121-8.
- Lang T, Johanning K, Metzler H, Piepenbrock S, Solomon C, Rahe-Meyer N, *et al.* The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. *Anesth Analg* 2009;108:751-8.
- Harr JN, Moore EE, Ghasabyan A, Chin TL, Sauaia A, Banerjee A, *et al.* Functional fibrinogen assay indicates that fibrinogen is critical in correcting abnormal clot strength following trauma. *Shock* 2013;39:45-9.
- Karkouti K, Callum J, Crowther MA, McCluskey SA, Pendergrast J, Tait G, *et al.* The relationship between fibrinogen levels after cardiopulmonary bypass and large volume red cell transfusion in cardiac

- surgery: An observational study. *Anesth Analg* 2013;117:14-22.
31. Pillai RC, Fraser JF, Ziegenfuss M, Bhaskar B. Influence of circulating levels of fibrinogen and perioperative coagulation parameters on predicting postoperative blood loss in cardiac surgery: A prospective observational study. *J Card Surg* 2014;29:189-95.
32. Essa Y, Zeynalov N, Sandhaus T, Hofmann M, Lehmann T, Doenst T, *et al.* Low fibrinogen is associated with increased bleeding-related re-exploration after cardiac surgery. *Thorac Cardiovasc Surg* 2017.
33. Kawashima S, Suzuki Y, Sato T, Kikura M, Katoh T, Sato S, *et al.* Four-group classification based on fibrinogen level and fibrin polymerization associated with postoperative bleeding in cardiac surgery. *Clin Appl Thromb Hemost* 2016;22:648-55.
34. Erdoes G, Gerster G, Colucci G, Kaiser H, Alberio L, Eberle B, *et al.* Prediction of post-weaning fibrinogen status during cardiopulmonary bypass: An observational study in 110 patients. *PLoS One* 2015;10:e0126692.
35. Mace H, Lightfoot N, McCluskey S, Selby R, Roy D, Timoumi T, *et al.* Validity of thromboelastometry for rapid assessment of fibrinogen levels in heparinized samples during cardiac surgery: A Retrospective, single-center, observational study. *J Cardiothorac Vasc Anesth* 2016;30:90-5.
36. Ranucci M, Baryshnikova E. Fibrinogen supplementation after cardiac surgery: Insights from the Zero-Plasma trial (ZEPLAST). *Br J Anaesth* 2016;116:618-23.
37. Tanaka KA, Egan K, Szlam F, Ogawa S, Roback JD, Sreeram G, *et al.* Transfusion and hematologic variables after fibrinogen or platelet transfusion in valve replacement surgery: Preliminary data of purified lyophilized human fibrinogen concentrate versus conventional transfusion. *Transfusion* 2014;54:109-18.