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 \( \leq 6 \text{ mm} \). 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\textsuperscript{®} 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\textsuperscript{®} 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 \( \leq 6 \text{ mm} \) (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/m\(^2\) 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\textsuperscript{®}, Baxter, S. A. Lessines, Belgium with a mixture of either 500 mL Ringer Acetate solution or 500 mL HES 6% 130/0,4 (Voluven\textsuperscript{®} or Volulyte\textsuperscript{®}, 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 \( \alpha \)-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\textsuperscript{®} SPSS\textsuperscript{®} 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
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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. 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. However, recently, other studies have failed to show a positive effect of human fibrinogen concentrate in cardiac surgery patients. Table 5 summarizes the design and the results of the 4 recent double-blinded, placebo-controlled

### 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, ×1000 μL) | 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
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 shows transference data. The table details the number of patients transfused with any product, red blood cells (RBC), fresh frozen plasma (FFP), platelets concentrate, packed RBC, and fibrinogen dose per kg (mg/kg) and (g) as well as the number of units.

| 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 |
| Number of patients transfused FFP | 27 (37) | 65 (89) | <0.001 |
| Number of patients transfused platelets concentrate | 32 (44) | 68 (93) | <0.001 |
| Packed RBC - number of units | 1 (0-2) | 4 (2-9) | <0.001 |
| FFP - number of units | 0 (0-3) | 5 (3-9) | <0.001 |
| Units platelets concentrate | 0 (0-7) | 21 (14-35) | <0.001 |
| Dose fibrinogen per kg (mg/kg) | 0 | 17 (13-26) | <0.001 |
| Dose fibrinogen (g) | 0 (0-0) | 1 (1-2) | <0.001 |
| 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.
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) | 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)       | 12 (11-14)        |     |
| FIBTEM MCF after fibrinogen use (mm)                    |               |                   |     |
| Multiplate test before fibrinogen use*                  |               |                   |     |
| AUC ADP                                                  | 289 (153-438) |                   |     |
| AUC ASPI                                                 | 293 (154-539) |                   |     |
| AUC TRAP                                                 | 513 (345-766) |                   |     |
| Platelet count (cells, ×1000/µL) 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|
| Platelet count (cells, ×1000/µL) 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 et al.[14] | Rahe-Meyer et al.[17] | Bileen et al.[18] | Jeppsson et al.[19] |
|------------------------|--------------------|-----------------------|-------------------|---------------------|
| Type of surgery        | Planned complex cardiac surgery with expected CPB time of ≥90 min | Elective aortic surgery+other cardiac procedures | Elective high-risk surgery | Elective CABG       |
| Number of patients analyzed for primary endpoint | Placebo (n=58) | Placebo (n=74) | Placebo (n=57) | Placebo (n=24) |
|                        | Fibrinogen (n=58) | Fibrinogen (n=78) | Fibrinogen (n=58) | Fibrinogen (n=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 | Fixed amount of fibrinogen administered |
| Dose fibrinogen administered fixed 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 | Based on post-CBP fibrinogen levels measured with the Clauss method and target fibrinogen level of 2.5 g/L | |
| 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.[13]

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.[15] 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.

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