

Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery

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Background. Normalization of plasma fibrinogen levels may be associated with satisfactory haemostasis and reduced bleeding. The aim of this retrospective study was to assess fibrinogen recovery parameters after administration of fibrinogen concentrate (Haemocomplettan[®] P) to patients with diffuse bleeding in cardiovascular surgery. Data on transfusion and patient outcomes were also collected.

Methods. Patient characteristic and clinical data were obtained from patient records. Results of the thromboelastometry (FIBTEM[®]) and of the standard coagulation tests, including plasma fibrinogen level, measured before surgery, before and after haemostatic therapy, and on the following day, were retrieved from laboratory records.

Results. Thirty-nine patients receiving fibrinogen concentrate for diffuse bleeding requiring haemostatic therapy after cardiopulmonary bypass were identified. The mean fibrinogen concentrate dose administered was 6.5 g. The mean fibrinogen level increased from 1.9 to 3.6 g litre⁻¹ (mean increment of 0.28 g litre⁻¹ per gram of concentrate administered); maximum clot firmness increased from 10 to 21 mm. The mean fibrinogen increase was 2.29 (SD 0.7) mg dl⁻¹ per mg kg⁻¹ bodyweight of concentrate administered. Thirty-five patients received no transfusion of fresh-frozen plasma (FFP) or platelet concentrate after receiving fibrinogen concentrate; the remaining four patients received platelet concentrate intraoperatively. Eleven patients received platelets, FFP, or both during the first postoperative day. No venous thromboses, arterial ischaemic events, or deaths were registered during hospitalization.

Conclusions. In this retrospective study, fibrinogen concentrate was effective in increasing plasma fibrinogen level, and contributed to the correction of bleeding after cardiovascular surgery.

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Most coagulation defects resulting from massive haemorrhage during surgery are caused by dilutional coagulopathy (loss, consumption, dilution, or both of coagulation factors, and reduction of clot stability by artificial colloids). Fibrinogen is the first coagulation factor to become critically reduced during major surgical blood loss.¹ In a pig model of dilutional coagulopathy, the increase in fibrinogen synthesis cannot compensate for the increased

breakdown even if blood loss is only moderate.² The observation that patients with higher fibrinogen levels experience fewer bleeding complications than those with low levels further highlights the importance of fibrinogen in the maintenance of haemostasis.^{3–5} In addition, cardiac surgery is associated with particular complications. For example, interactions with the extracorporeal surfaces of the heart–lung machine during cardiopulmonary bypass

(CPB) causes marked activation of the coagulation system, platelet activation, and platelet destruction.⁶

Fresh-frozen plasma (FFP) contains all plasma coagulation factors, but the concentration of fibrinogen is not sufficient for the treatment of severe deficiency.^{7 8} Cryoprecipitate is a more concentrated source of fibrinogen available in the USA and UK. However, its use is poorly standardized,⁹ and safety concerns led to its withdrawal from most European countries. Fibrinogen concentrate was recently licensed in the USA and is well established in Central Europe for the treatment of congenital fibrinogen deficiency. In Central Europe, it is also increasingly used for management of acquired fibrinogen deficiency.^{8 10–15}

Administration of fibrinogen concentrate has been shown to improve clot firmness and reduce blood loss using *in vitro* and pig models of dilutional coagulopathy.^{16 17} Furthermore, a high dose of fibrinogen concentrate was more effective than transfusion of platelet concentrates in decreasing the rate of blood loss and prolonging survival time in a pig model,¹⁸ indicating that raising fibrinogen levels might compensate for low platelet counts. This observation was confirmed in a retrospective analysis of clot quality in 904 thrombocytopenic patients.¹⁹ Clinical studies have provided evidence for the efficacy and tolerability of fibrinogen concentrate in congenital fibrinogen deficiency,^{20 21} and data on its use in patients with acquired deficiency in a variety of surgical settings are beginning to emerge.^{8 10 12–15 22–24} A recently published randomized placebo-controlled trial showed that administration of fibrinogen concentrate in patients undergoing radical cystectomy reduced the requirement for postoperative transfusion.¹¹

This retrospective study assessed recovery parameters of fibrinogen after administration of fibrinogen concentrate to patients with diffuse bleeding after weaning from CPB in cardiac surgery. Data on transfusion of allogeneic blood products, local reactions, major thromboembolic complications, 24 h survival, and survival until discharge from hospital were also collected.

Methods

Study design and patient population

This was an open-label, uncontrolled, retrospective study conducted in the cardiothoracic surgery department of Hannover Medical School between December 2006 and December 2008. After research ethics board approval, data were obtained from pharmacy-dispensing records, anaesthesia records, and standard coagulation laboratory records. The analysis included all patients who received fibrinogen concentrate for active bleeding who also had their plasma fibrinogen levels documented before and after fibrinogen concentrate administration. Data from patients

with concomitant administration of haemostatic medication containing fibrinogen (FFP), non-elective or emergency intervention, age <18 yr, and terminal illness were excluded from the analysis.

Evaluation

The following information was collected: age, gender, weight, BMI, surgery details, and any adverse events documented in the clinical records. In addition, standard laboratory test results [fibrinogen, prothrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, haemoglobin, and haematocrit] were collected from the laboratory records. The time points included were: before surgery (baseline), before haemostatic therapy (at the end of CPB), before the end of surgery, and the following day.

Fibrinogen analysis

Thromboelastometric measurement of the fibrin-based clot was performed using the FIBTEM[®] test as described previously.²⁵ The maximum clot firmness (MCF) parameter reflects the total firmness of the clot formed in the presence of platelet inhibition with cytochalasin D. Plasma fibrinogen levels were determined using the Clauss method (STA-R device and reagents, Diagnostica Stago, Asnieres, France). Median increase (response) in mg dl^{-1} per mg kg^{-1} bodyweight of fibrinogen was calculated, and also the median increment (g litre^{-1}) per 1 g fibrinogen concentrate administered. *In vivo* recovery was calculated as the actual increase in fibrinogen level divided by the expected increase in fibrinogen ($\text{mg dl}^{-1} \times 100$), where the expected increase in fibrinogen was the dose of fibrinogen (mg) divided by the plasma volume (ml). The plasma volume was calculated as $70 \times \text{bodyweight (kg)} \times (100 - \text{haematocrit}) \times 100^{-1}$.

Clinical management

Anaesthesia was induced with etomidate 0.3 mg kg^{-1} , fentanyl $8 \text{ } \mu\text{g kg}^{-1}$, and cisatracurium 0.2 mg kg^{-1} . During the induction of anaesthesia, patients received lactated Ringer's solution and gelatin polysuccinate (Gelafundin[®] 0.026; Serumwerk, Bernburg, Germany). For maintenance of anaesthesia, sevoflurane was titrated to an end-tidal concentration of 1–2% until institution of CPB. For the duration of CPB, propofol was infused at $50\text{--}80 \text{ } \mu\text{g kg}^{-1} \text{ min}^{-1}$ and additional $4 \text{ } \mu\text{g kg}^{-1}$ boluses of fentanyl were administered every 30 min for the duration of CPB. CPB was established after cannulation and administration of 400 IU kg^{-1} of heparin (Heparin-Natrium-2500-ratiopharm[®], Merckle GmbH, Blauberen, Germany); moderate hypothermia (34°C) was used. Aprotinin was used in all but three patients, who received tranexamic acid.

After weaning from bypass, administration of protamine and completion of surgical haemostasis, virally inactivated, pasteurized fibrinogen concentrate (Haemocompletan[®]

P, CSL Behring, Marburg, Germany) was administered as a first-line coagulation therapy to patients with diffuse bleeding. The dosing of fibrinogen concentrate was guided by FIBTEM thromboelastometry.^{13 14} The fibrinogen dose (g) administered to increase FIBTEM MCF was calculated using the formula (target FIBTEM MCF–actual FIBTEM MCF)×bodyweight/140, which corresponds to ~0.5 g of fibrinogen concentrate needed to raise MCF by 1 mm in a 70 kg patient. Fibrinogen concentrate was administered regardless of platelet count; platelet concentrate was administered as a second-line haemostatic therapy. Red blood cells (RBCs) were transfused to maintain haematocrit values between 23% and 25% on CPB and above 28% after CPB after blood from the extracorporeal circulation system was re-infused. Transfusion in the intensive care unit (ICU) was administered when the drainage volume was higher than 400 ml h⁻¹ and consisted of platelet concentrate for platelet count <100×10³ µl⁻¹ and FFP for prolongation of PT >1.5 times normal.

Statistical analysis

Normality of data distribution was tested using the Kolmogorov–Smirnov test. Results are expressed as mean and standard deviation (SD), median (25th percentile, 75th percentile), or number and percentage. Differences between time points were analysed using the paired Student's *t*-test with Bonferroni's correction for repeated measurements. Statistical significance was defined as *P*<0.05.

Results

Thirty-nine patients treated for active bleeding with fibrinogen concentrate were identified. Of these, 34 (87%) were male; mean age was 58 (range: 25–78) yr; mean weight was 85 (SD 17.3) kg; and mean BMI was 27.5 (4.6) kg m⁻². Surgical procedures are summarized in Table 1; most patients underwent aortocoronary bypass (ACB), aortic valve and ascending aortic aneurysm surgery, or thoracoabdominal aortic aneurysm surgery. Aspirin intake within 5 days of surgery was reported in six patients undergoing ACB (60%) and in four patients undergoing repeat ACB (80%). One patient undergoing repeat ACB was reported to have taken clopidogrel within 5 days of surgery.

At the end of CPB, PT and aPTT were significantly prolonged, and platelet count, haemoglobin, and haematocrit were significantly reduced compared with baseline values (Table 2). After the administration of fibrinogen concentrate, there were no significant changes in platelet count, haemoglobin, or haematocrit. PT was slightly shortened (from 20.8 to 20.1 s), whereas aPTT was prolonged (from 26.6 to 41.5 s). Before administration of fibrinogen concentrate, mean Clauss fibrinogen was 1.9 (0.6) g litre⁻¹ (Table 2, Fig. 1). The mean dose of fibrinogen concentrate administered was 6.5 (1.6) g or 78 (20) mg kg⁻¹. The first

Table 1 Type and details of surgery for the 39 patients included in the study. AV–AA, aortic valve and ascending aortic aneurysm; ICU, intensive care unit; TAAA, thoracoabdominal aortic aneurysm

Type of surgery [n (%)]	
Aortocoronary bypass	10 (25.5)
Re-aortocoronary bypass	5 (13)
TAAA	10 (25.5)
Re-TAAA	1 (3)
AV–AA	13 (33)
Surgery details [mean (SD) or n (%)]	
CPB duration (min)	109.3 (45.1)
Lowest temperature on CPB (°C)	33.4 (2.7)
ICU time to extubation (h)	34.2 (104.1)
ICU time (h)	50.4 (102.8)
Re-exploration for bleeding	3 (8)
24 h postoperative drainage volume (ml)	623.6 (400)
Postoperative hospital stay (days)	11.7 (6.3)

post-therapy sample was obtained before the end of surgery, <1 h after fibrinogen concentrate administration. At this time, mean Clauss fibrinogen level was 3.6 (0.7) g, which was significantly higher (*P*<0.001) than at the end of CPB (Table 2). Of importance, this value did not differ significantly from the baseline value of 3.3 (1.0) g litre⁻¹. The mean Clauss fibrinogen level increased in all patients after fibrinogen concentrate administration [mean absolute increase 1.7 (0.5) g litre⁻¹; Table 3]. Fibrinogen recovery is detailed in Table 3. The calculated *in vivo* recovery of fibrinogen was >100%. FIBTEM MCF increased from 10.1 (3.7) to 20.7 (3.9) mm (Table 2), and the mean fibrinogen dose required to increase FIBTEM MCF by 1 mm was 7.6 (2) mg kg⁻¹ bodyweight (Table 3).

Intraoperative allogeneic blood products included RBC (administered to two patients) and platelet concentrate (administered to four patients in whom bleeding had not ceased after fibrinogen concentrate therapy). No FFP was transfused intraoperatively. Thirty-five patients (90%) received no intraoperative transfusions after the administration of fibrinogen concentrate.

Twenty-eight patients (72%) received no postoperative transfusions. During the first postoperative day, one patient received only RBC transfusion, whereas 11 patients received haemostatic therapy: five patients received platelet concentrate and FFP, and six patients received only FFP. Of these 11 patients, eight received haemostatic therapy according to the intensivist's clinical judgement and ICU standards. In the remaining three patients, re-thoracotomy was performed because of suspected bleeding. In all three of these cases, a surgical source of bleeding was identified, and FFP and platelet concentrates were administered. No venous thromboses, arterial ischaemic events, or deaths were identified up to the time when patients were discharged from hospital.

Discussion

In the present retrospective analysis, administration of a mean dose of 6.5 g of fibrinogen concentrate in

Table 2 Standard laboratory data at different time points. Values are presented as the mean (SD). PT, prothrombin time; aPTT, activated partial thromboplastin time; CPB, cardiopulmonary bypass; FIBTEM, thromboelastometric test investigating fibrin-based clot; MCF, maximum clot firmness. *P*-values: ¹end of CPB vs baseline, ²after fibrinogen vs end of CPB, ³first postoperative day vs after fibrinogen; **P*<0.05; ***P*<0.001

Parameter	Mean (SD) (<i>n</i> =39)			
	Baseline	End of CPB (before fibrinogen concentrate therapy) ¹	After fibrinogen concentrate therapy, before the end of surgery ²	First postoperative day ³
PT (s; normal range, 11–13.5)	14.1 (1.2)	20.8 (3.1)**	20.2 (3.9)*	16.6 (1.7)**
aPTT (s; normal range, 26–35)	30.3 (2.8)	36.6 (11.5)**	42.0 (11.4)*	37.3 (9.8)*
Platelet count (10 ³ μl ⁻¹ , normal range, 150–450)	192.6 (52.2)	101.5 (49.5)**	104.0 (38.7)	121.5 (39.6)*
Haemoglobin (g dl ⁻¹ , normal range, 13.5–17.5)	13.1 (1.4)	9.9 (1.1)**	9.7 (1.2)	10.4 (1.1)*
Haematocrit (%; normal range, 41.5–50.4)	37.8 (3.9)	28.5 (3.1)**	27.7 (3.4)	30.5 (3.4)*
FIBTEM MCF (mm, normal range 9–25)	15.5 (4.9)	10.1 (3.7)**	20.7 (3.9)**	22.3 (2.3)*
Fibrinogen (g litre ⁻¹ , normal range, 2.0–4.5)	3.3 (1.0)	1.9 (0.6)**	3.6 (0.7)**	4.5 (0.7)**

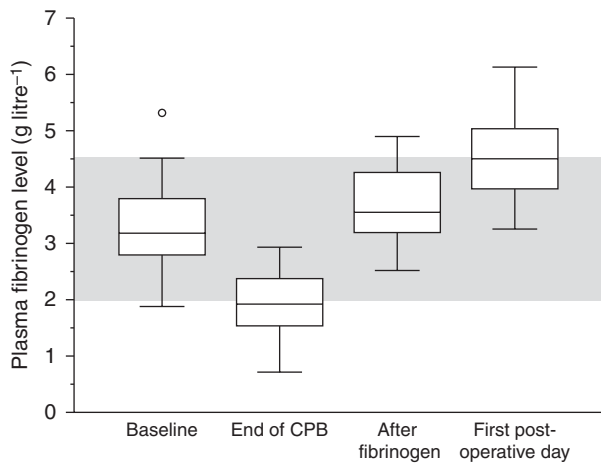


Fig 1 Box-and-whisker plots of plasma fibrinogen levels measured using the Clauss method at baseline, end of CPB, after administration of fibrinogen concentrate, and during the first postoperative day. The boxes represent the lower (25th) and upper (75th) quartiles, the horizontal line represents the mean, the whiskers extend to 95% confidence intervals for the mean, and the circle represents an outlier. Grey shading indicates the normal range of plasma fibrinogen levels.

Table 3 Recovery parameters of the administered fibrinogen concentrate. FIBTEM, thromboelastometric test investigating fibrin-based clot; MCF, maximum clot firmness; SD, standard deviation

Parameter	Mean (SD) (<i>n</i> =39)
Absolute increase in fibrinogen (g litre ⁻¹)	1.7 (0.5)
Fibrinogen increment (g litre ⁻¹ per 1 g fibrinogen administered)	0.28 (0.1)
Increase (response) in mg dl ⁻¹ per substituted mg kg ⁻¹ bodyweight	2.3 (0.7)
<i>In vivo</i> recovery (%)	114 (32)
Mean dose of fibrinogen to increase FIBTEM MCF by 1 mm (mg kg ⁻¹ bodyweight)	7.6 (2.0)

cardiovascular surgery patients with diffuse bleeding after weaning from CPB was followed by an 89% increase in the fibrinogen plasma level and *in vivo* recovery of 114%. Our results showed that the administration of a mean dose of fibrinogen concentrate of 6.5 g increased plasma fibrinogen

levels by a mean of 1.7 g litre⁻¹, with an increment of 2.3 g litre⁻¹ per substituted mg kg⁻¹ bodyweight. This finding is not in agreement with other studies investigating the administration of fibrinogen concentrate for haemostatic therapy in acquired fibrinogen deficiency. In the observational study performed by Danes and colleagues⁸ investigating 69 patients suffering from various forms of acquired severe hypofibrinogenaemia, a mean absolute increase of 1.09 g litre⁻¹ of plasma fibrinogen was measured 24 h after a median dose of 4 g of fibrinogen concentrate (Table 4). In another retrospective study of 43 patients, Fenger-Eriksen and colleagues²² showed an increase in fibrinogen of 1.01 g litre⁻¹ with only half the dose (median 2 g) of fibrinogen concentrate (Table 4). The differences in the increase of fibrinogen plasma concentration may reflect differences between the study populations such as underlying clinical conditions (e.g. sepsis, haematological malignancy, and liver insufficiency),⁸ mean age (52 and 49.5 yr in the studies by Danes and colleagues⁸ and Fenger-Eriksen and colleagues,²² respectively), and the proportion of paediatric patients (2.9% and 9.3% in the studies by Danes and colleagues⁸ and of Fenger-Eriksen and colleagues,²² respectively). The patients included in our study were all aged >18 yr [mean age 58 (SD 11) yr], and cardiovascular surgery was the only clinical condition. Furthermore, our retrospective analysis excluded patients receiving additional medication containing fibrinogen (i.e. FFP) between the pre- and post-therapy analysis of fibrinogen concentration. Administration of haemostatic products containing fibrinogen in addition to fibrinogen concentrate between the pre- and post-therapy time could have influenced the fibrinogen recovery parameters reported previously. It is difficult to estimate whether recovery values would have been higher or lower in the previous reports in the absence of FFP administration. The concentration of fibrinogen in FFP varies between units but is generally lower than the plasma concentrations reached in our patients. Above a target level of 2.25 g litre⁻¹, which is the mean concentration of fibrinogen in plasma thawed after more than 24 h of storage,²⁶ FFP is likely to act as a diluent and decreases the plasma fibrinogen concentration.

Table 4 Previously published data on plasma fibrinogen recovery in patients with acquired hypofibrinogenaemia. N/R, not reported

	Study		
	Danes and colleagues ⁸	Fenger-Eriksen and colleagues ²²	Weinkove and Rangarajan ¹⁵
Number of patients treated	69	43	30
Fibrinogen dose (g)	4	2	4
Absolute dose range (g)	0.5–8	1–5	2–14
Average increase of plasma fibrinogen (g litre ⁻¹)	1.09	1.01	1.19
Median (range) increment per 1 g fibrinogen concentrate (g litre ⁻¹)	0.28 (0–3.7)	N/R	0.25 (0.07–0.84)
<i>In vivo</i> recovery (%)	109.1	N/R	N/R

Recovery values >100% (e.g. 109% reported by Danes and colleagues⁸ and 114% in the present study) can be explained by the slightly hypovolaemic conditions that commonly occur after surgery. Prolonged bleeding in the ICU or a postoperative increase in fibrinogen as part of the acute phase reaction can also influence plasma fibrinogen over a time frame of hours.^{8 15 22} Earlier measurement (e.g. within 1 h of administration, as in the present study) might overcome this limitation. Values of recovery above 100% also raise the question whether the amount of fibrinogen present in the vials was higher than 1 g, the amount indicated on the label. Batches of Haemocomplettan P vary slightly in fibrinogen content, since this concentrate is a biological product fractionated from FFP (cryoprecipitate). The packet insert indicates a range of 900–1300 mg per 1 g vial. However, this does not represent the actual variation in the amount of fibrinogen; instead, this is the theoretical variation allowed. We performed a review of the certificates of analysis of fibrinogen concentrate batches and found a high degree of consistency in fibrinogen content: vials were overfilled by a mean 8.75% at the beginning of the shelf-life to compensate for several factors that lead to loss of fibrinogen during administration: fibrinogen solution remaining in the vial, transfer from the glass vial into syringes, fluid remaining in the perfusion line, etc. In the present report, recovery was calculated according to the label (1 g per vial) and not according to the actual amount of fibrinogen administered, because in clinical practice, the concentrate is generally dosed according to the label.

In our clinic, fibrinogen concentrate is administered considerably more rapidly (e.g. 6 g in 1–2 min) for severe bleeding occurring intraoperatively than in a non-acute setting (e.g. congenital deficiency) in order to obtain a prompt haemostatic response. This infusion rate is higher than the rate recommended in the package insert (5 ml min⁻¹, representing a 60 min infusion time for 6 g). However, it is unclear how different infusion rates influence the increase in fibrinogen concentration measured after 1 h; further investigations are warranted for the perioperative setting where rapid correction of severe bleeding is required.

The mean dose of 6.5 g fibrinogen concentrate administered here was higher than the doses administered in

acquired hypofibrinogenaemia in other studies, including cardiac surgery patients.^{8 10 15 23} In the guidelines recently published by the German Medical Association, it is suggested that adults will generally require a single dose of 3–6 g of fibrinogen concentrate.²⁷ Importantly, the mean level of fibrinogen after administration of fibrinogen concentrate was comparable with baseline levels, which correspond to levels reported for healthy subjects of similar age.²⁸ The high-normal target level of fibrinogen was chosen based on observations regarding the protective role of high fibrinogen concentration against bleeding in cardiac and non-cardiac settings.^{3–5} On the basis of the results of previous *in vitro* investigations,^{18 19} high fibrinogen concentration might have compensated for decreased platelet counts with regard to clot firmness.

The administration of fibrinogen concentrate and the calculation of recovery parameters is generally based on the plasma fibrinogen level measured using the Clauss method (turbidimetric read-out). In our department, however, administration of fibrinogen concentrate is most often guided by the thromboelastometric FIBTEM test because of its rapidity and its reflection of the mechanical strength of the clot. There are reports on the use of FIBTEM to guide haemostatic therapy in several settings, including orthopaedic surgery, trauma, and cardiovascular surgery.^{10 13 14 29} MCF target levels above 7 mm have been considered for orthopaedic surgery,¹⁰ whereas in cardiovascular surgery, a considerably higher target has been discussed (22 mm).^{13 14} There is currently no evidence for these target levels, and randomized controlled trials investigating this therapeutic approach appear desirable. Nevertheless, FIBTEM appears to be a valuable means of guiding fibrinogen concentrate therapy in the perioperative setting. Although a correlation between plasma fibrinogen concentration and FIBTEM MCF has been reported,³⁰ neither FIBTEM nor the Clauss method measure fibrinogen concentration directly. The Clauss method measures the time to fibrin formation and compares it with a calibration curve.³¹ The result is therefore a clotting time, from which the concentration of fibrinogen can be derived. When obtained using a photo-optical technique, as in the present report, the result may be affected by many functional fibrinogen-independent factors, such as fibrinogen degradation products that have an anticoagulant effect, fibrin degradation products, haemodilution with hydroxyethyl

starches,³² or factors that influence turbidity (e.g. lipid concentration in the plasma sample, bile pigment, and free haemoglobin). Fibrinogen values obtained when using the Clauss method are therefore prone to inaccuracy. FIBTEM, a test for assessing the elasticity of the fibrin clot under platelet inhibition by cytochalasin D, is more a measurement of fibrin quality rather than a fibrinogen measurement. FIBTEM MCF is mainly dependent on fibrinogen concentration, but as with the Clauss assay, it is subject to the influence of fibrinogen-independent factors. FXIII appears to be one of these factors.³³ The present data show that after therapy, the mean fibrinogen increased to 189% of the pre-therapy value, whereas the mean FIBTEM MCF increased to 200%. The apparently higher increase in FIBTEM MCF may have been related to small amounts of FXIII in the fibrinogen concentrate (i.e. 50 IU FXIII per 1 g fibrinogen concentrate). As FXIII has been shown to help maintain clot firmness in haemodilution,³⁴ it appears necessary to investigate further its haemostatic role in the present setting.

The records of the patients included in the study showed no venous thromboses or arterial ischaemic events. Regarding the safety of fibrinogen concentrate administration, a 22 yr pharmacovigilance programme and a systematic review of clinical studies indicated that the thrombogenic potential of Haemocomplettan® P is low.³⁵ In fact, given its role as a substrate for formation of the fibrin net, fibrinogen may play an important antithrombotic role. Fibrin, known as antithrombin I, acts by sequestering thrombin in the incipient clot, reducing the activity of the bound thrombin, and localizing the subsequent processes of clot formation.³⁶ Sufficient formation of the fibrin net may be beneficial at the end of CPB, when antithrombin levels are decreased,³⁷ and reversal of heparinization is induced with protamine.

Nevertheless, caution is required when administering fibrinogen concentrate for the treatment of bleeding after ACB, because there are few data on the influence of this therapy on graft patency or on its safety in this setting. In a prospective study of 10 ACB patients, prophylactic administration of fibrinogen concentrate increased baseline fibrinogen concentration of 2.9 by 0.7 g litre⁻¹, and no clinically relevant postoperative thrombotic events were observed.²⁴ High preoperative fibrinogen values (>3.5 g litre⁻¹) in ACB have been shown to predict postoperative mortality of all cause, but not the mortality from cardiac cause or the need for myocardial vascularization,³⁸ supporting the hypothesis that fibrinogen was a marker of inflammation, rather than a cause of thrombosis in these patients. On the other hand, decreased preoperative fibrinogen values have been shown to correlate with bleeding after ACB,⁵ possibly because they lead to low fibrinogen values when weaning from CPB. In contrast to the prophylactic approach, some clinicians favour administration of fibrinogen concentrate only for therapy of overt bleeding, as in the present study. It remains to be established whether administering fibrinogen concentrate as

prophylaxis or for correction of bleeding in a dosage adjusted according to bodyweight, actual fibrinogen level or fibrin-based clot firmness is a more viable strategy when using fibrinogen concentrate as haemostatic therapy for severe bleeding post-CPB.

One limitation of the current study is variation in the type of cardiac surgery. Also, bleeding and necessity for transfusion were judged clinically, which could introduce bias. A further limitation of the study is that the fibrinogen recovery parameters were calculated from values obtained towards the end of surgery, and not immediately after administration of fibrinogen concentrate. Infusion of colloids, crystalloids, or blood from cell-saver could have influenced the recovery parameters. However, with bleeding already corrected by the haemostatic therapy, the patients were in a stable condition at this time, and the impact of plasma loss or replacement would have been limited. Furthermore, it is important to keep in mind that the comparability of pharmacokinetic data presented in different reports is limited if different methods of fibrinogen measurement are used.³⁹ A number of different assays based on the Clauss method are commercially available, and they vary in thrombin strength, buffer composition, inclusion of inhibitors of heparin and fibrinogen degradation products, calibration method, and dilution range. Even when calibrated correctly, Clauss assays can differ up to 50%.^{32 40} Recently, Fenger-Eriksen and colleagues⁴¹ showed that the results of Clauss measurement differ significantly in the presence of colloid plasma expander when using different automated coagulation analysers. Variability can also be introduced by different commercially available calibrators,⁴² or by heterogeneity of fibrinogen (high molecular weight fraction/low molecular weight fraction) in different patient groups compared with the calibration material.^{43 44} Each of these factors alone might not be clinically relevant in the perioperative setting, but taken together they could invalidate comparisons between studies.

In conclusion, this retrospective analysis showed that fibrinogen concentrate administered for haemostatic therapy in cardiovascular surgery was effective in increasing the plasma fibrinogen level and contributed to the correction of bleeding. Prospective investigation of this therapeutic approach appears warranted.

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Conflict of interest

C.S. and H.S. received speaker honoraria from Pentapharm GmbH and CSL Behring. N.R.-M. received speaker honoraria from, and was a member of advisory boards for, CSL Behring. C.S. and N.R.-M. are investigators in the phase IIb study NCT 00701142 sponsored by CSL Behring.

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