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Original Article

Fibrinogen concentrate vs. fresh frozen plasma for the management of coagulopathy during thoraco-abdominal aortic aneurysm surgery: a pilot randomised controlled trial

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Summary

Major vascular surgery is frequently associated with significant blood loss and coagulopathy. Existing evidence suggests hypofibrinogenaemia develops earlier than other haemostatic deficiencies during major blood loss. The purpose of this study was to assess whether the use of an infusion of fibrinogen concentrate to prevent and treat hypofibrinogenaemia during surgery resulted in satisfactory haemostasis, removing or reducing the need for blood component transfusion. Twenty patients undergoing elective extent-4 thoraco-abdominal aortic aneurysm repair were randomly allocated to receive either fresh frozen plasma or fibrinogen concentrate to treat hypofibrinogenaemia during surgery. Coagulation was assessed during and after surgery by point-of-care and laboratory testing, respectively, and treatment was guided by pre-defined transfusion triggers. Despite blood losses of up to 11,800 ml in the patients who received the fibrinogen concentrate, none required fresh frozen plasma during surgery, and only two required platelet transfusions. The median (IQR [range]) allogeneic blood component administration during surgery and in the first 24 h postoperatively was 22.5 (14–28 [2–41]) units in patients allocated to fresh frozen plasma vs. 4.5 (3–11[0–17]) in patients allocated to fibrinogen concentrate ($p = 0.011$). All patients in both groups were assessed by the surgeon to have satisfactory haemostasis at the end of surgery. Mean (SD) postoperative fibrinogen concentrations were similar in patients allocated to fresh frozen plasma and fibrinogen concentrate (1.6 (0.3) $g.l^{-1}$ vs. 1.6 (0.2) $g.l^{-1}$; $p = 0.36$) but the mean (SD) international normalised ratio and activated partial thromboplastin time ratio were lower in patients allocated to fresh frozen plasma (1.1 (0.1) vs. 1.8 (0.3); $p < 0.0001$ and 1.1 (0.2) vs. 1.7 (0.5); $p = 0.032$, respectively). Fibrinogen concentrate may be used as an alternative to fresh frozen plasma in the treatment of coagulopathy during thoraco-abdominal aortic aneurysm repair.

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Introduction

Open thoraco-abdominal aortic aneurysm repair is associated with major haemorrhage and the development of coagulopathy during surgery [1]. Causes of coagulopathy include haemodilution and abdominal visceral ischaemia leading to deficiencies of fibrinogen and other coagulation

factors, thrombocytopenia and excessive fibrinolysis. The intra-operative administration of heparin and pre-operative antiplatelet drugs may also impair haemostasis.

Impairment of haemostasis is commonly treated with the transfusion of fresh frozen plasma (FFP), cyoprecipitate and platelet concentrates [2]. However, blood component transfusions may result in adverse effects including the transmission of infection, immunosuppression and lung injury [3]. Furthermore, delays in obtaining blood components may occur because FFP and cryoprecipitate must be thawed before administration and platelet concentrates, which have a shelf life of only a few days [4], are sometimes in short supply and, in some hospitals, not immediately available on-site.

After massive haemorrhage and haemodilution, a deficiency of fibrinogen is likely to result in impaired haemostasis before thrombocytopenia or deficiencies of other coagulation factors become severe enough to do so [5–7]. In addition, fibrin polymerisation may be impaired by haemodilution, particularly when synthetic colloids are administered [8]. Fibrinogen may be replaced by transfusing FFP or cryoprecipitate but an alternative is to give fibrinogen concentrate. Fibrinogen concentrate is derived from pooled human plasma which is purified, treated to inactivate pathogens and freeze dried. It may be stored at room temperature in the operating room and then dissolved in sterile water when required. Data exist supporting its safety [9, 10] and it is thought to be associated with a lower risk of adverse effects when compared with blood components [11].

A standard adult therapeutic dose of cryoprecipitate (two pools) is produced from 10 donors, contains around 3.3 g of fibrinogen and has a volume of approximately 380 ml [4]. A standard adult therapeutic dose of FFP (four units) is from four donors, typically contains 2.8 g of fibrinogen and has a larger volume of approximately 1070 ml [12, 13]. Fibrinogen concentrate is supplied as 1 g fibrinogen to be prepared in 50 ml of sterile water.

We hypothesised that the principal deficiency resulting in impaired haemostasis during thoraco-abdominal aortic aneurysm surgery is fibrinogen deficiency and that maintaining the plasma fibrinogen concentration within the normal range by infusion of fibrinogen concentrate would result in satisfactory haemostasis while avoiding or reducing the need for blood component transfusion to correct haemostasis.

In a single-blind pilot, we compared the use of our standard treatment of FFP transfusion with fibrinogen concentrate infusion in patients undergoing elective repair of extent-4 thoraco-abdominal aortic aneurysms. In each case, administration was guided by frequent point-of-care testing of haemostasis by ROTEM® thromboelastometry (Tem Innovations GmbH, Munich, Germany) [14].

Methods

This single-centre study was approved by a research ethics committee, and clinical trial authorisation was granted by the Medicines and Healthcare products Regulatory Agency (MHRA). Written informed consent was obtained from all participants.

We studied patients undergoing elective repair of extent-4 thoraco-abdominal aortic aneurysm between June 2010 and August 2013. We included patients with mild pre-operative thrombocytopenia (platelet count 100–150 $\times$ $10^9.l^{-1}$) and those taking aspirin or dipyridamole. We did not study patients with any of the following criteria: pre-operative coagulation abnormality (international normalised ratio (INR) and/or activated partial thromboplastin time ratio (APTTr) above 1.2); pre-operative therapy with an oral anticoagulant drug or P2Y12 inhibitor antiplatelet drug; and any haematological disorder associated with an increased bleeding tendency, for example, haemophilia or von Willebrand's disease.

An extent-4 thoraco-abdominal aortic aneurysm involves the entire abdominal aorta. Repair requires clamping the lower descending thoracic aorta at the level of the diaphragm and a period of ischaemia of the liver, kidneys and bowel. There may also be ischaemia of the anterior part of the spinal cord because the upper lumbar arteries make an important contribution to the blood supply to the anterior spinal artery in some patients. The surgical and anaesthetic technique used in our institution for extent-4 thoraco-abdominal aortic aneurysm repair has been described previously [15]. In summary, combined epidural and general anaesthesia is used, along with arterial and central venous pressure monitoring; the arterial line is not heparinised. An underbody water blanket and forced air warmer are used to reduce the patient's body temperature to approximately 32 °C before the period of abdominal visceral ischaemia and then to raise the temperature to over 36 °C before awakening the patient after surgery. Two cell savers (Haemonetics Corporation, Braintree, MA, USA) are used in each case for salvage and autotransfusion of red cells, and acid-citrate-dextrose (ACD) is used as the anticoagulant for the salvaged blood. However, fibrinogen, other coagulation factors and platelets are lost during the process of separating and washing the red cells and are not returned to the patient in significant quantities. Abdominal visceral ischaemia, blood loss and the administration of citrated blood components and other intravenous (i.v.)

fluids result in metabolic acidaemia, hypocalcaemia, hypomagnesaemia and hyperglycaemia during surgery. These abnormalities are prevented/corrected by infusions of sodium bicarbonate, calcium, magnesium and insulin with the infusion rates adjusted according to results from point-of-care testing.

Patients were randomly allocated using sealed envelopes to receive an infusion of either FFP or fibrinogen concentrate during surgery in order to prevent/correct hypofibrinogenaemia. Arterial blood samples were drawn at pre-defined time-points for immediate point-of-care testing with ROTEM thromboelastometry and blood gas analysis, and simultaneous samples were taken for later laboratory studies of coagulation (time-point 1: baseline sample in anaesthetic room, before the administration of any fluids; time-point 2: start of surgery; time-points 3–10: every 60 min after the start of surgery until aortic cross-clamping, at aortic cross-clamping, then every 30 min, reducing the frequency to every 60 min later in surgery once majority of bleeding had occurred; time-point 11: 2 h after the end of surgery; and time-point 12: 24 h after the end of surgery).

The infusions were adjusted on the basis of the FIBTEM test results with the goal of maintaining/restoring the plasma fibrinogen concentration within the normal range. They were commenced if the FIBTEM A10 was below the normal range, that is, < 8 mm or if the expectation was that it had fallen below the normal range because the most recent result was at the lower end of the normal range and there had been subsequent significant blood loss. The FFP group received FFP at an initial rate of 15 $ml.kg^{-1}.h^{-1}$ (approximately 40 $mg.kg^{-1}.h^{-1}$ of fibrinogen[17]) and the fibrinogen group received fibrinogen concentrate at 40 $mg.kg^{-1}.h^{-1}$. Both infusion rates were doubled, left unchanged or halved according to subsequent FIBTEM results. The infusions were stopped if FIBTEM A10 was ≥ 8 mm and there was no significant ongoing bleeding.

Pre-defined triggers were used for the transfusion of allogeneic packed red cells (PRC), platelet concentrates and additional FFP (as a source of coagulation factors other than fibrinogen) intra-operatively and for 24 h postoperatively (Table 1). Cryoprecipitate was not used. Tranexamic acid was given only if ROTEM tests indicated excessive fibrinolysis, defined as maximum lysis (ML) > 20% in the EXTEM test but not in the APTEM test. The ROTEM analyser was used only in the operating room so postoperative triggers were based on laboratory results. Fibrinogen concentrate was not used after surgery.

The decision as to the volume of fluid to give during surgery was guided by arterial and central venous pressures, pulse pressure and stroke volume variation during positive pressure ventilation, and blood pressure and stroke volume response to fluid challenges (measured using a LiDCOplus monitor (LIDCO, London, UK)). Crystalloids (Hartmann's solution) and colloids (a mixture of Geloplasma® (Fresenius Kabi, Louviers, France) and Volulyte® (Fresenius Kabi) were administered during surgery in an overall ratio of approximately 1:1. In the fibrinogen group, 250 ml human albumin solution 4.5% was administered with every 1 g of fibrinogen concentrate. Intravenous unfractionated heparin (70 $iU.kg^{-1}$) was given before aortic clamping and was not reversed.

Table 1 Intra and postoperative transfusion triggers.

Abnormality	Trigger	Treatment
Intra-operative		
Low coagulation factors (other than fibrinogen)	EXTEM CT > 100 s and/or HEPTEM CT > 300 s despite FIBTEM A10 ≥ 8 mm	FFP
Thrombocytopenia	1. EXTEM A10 < 30 mm despite FIBTEM A10 ≥ 8 mm or 2. EXTEM A10 < 22 mm.	Platelets
Anaemia	Haemoglobin < 90 $g.l^{-1}$	Packed red cells
Postoperative		
Hypofibrinogenaemia	Fibrinogen < 1.0 $g.l^{-1}$	FFP or cryoprecipitate
Low coagulation factors (other than fibrinogen)	INR > 2.0 and/or APTTr > 2.0	FFP
Thrombocytopenia	Platelet count < 50 × $10^9.l^{-1}$	Platelets
Anaemia	Haemoglobin < 90 $g.l^{-1}$	Packed red cells

FFP, fresh frozen plasma; CT, clotting time; INR, international normalised ratio; APPTr, activated partial thromboplastin time ratio.

Intra-operative blood loss, blood component and blood product administration, and fluid administration was documented at each sampling point. Intra-operative blood loss was calculated by adding the volume aspirated into the cell salvage and discard suction reservoirs to the blood loss on swabs and packs (calculated from wet weight minus dry weight) and then subtracting the volume of irrigation fluid and ACD anticoagulant used.

The primary outcome measure was the number of allogeneic blood components transfused during surgery and up to 24 h postoperatively. Secondary outcome measures were: laboratory coagulation and haemoglobin test results 2 h after the end of surgery; bleeding or thrombotic complications; 30-day all-cause mortality; duration of critical care stay; and duration of hospital stay.

Descriptive and inferential statistical analysis was carried out using GraphPad Prism v6.07 (GraphPad Software, San Diego, CA, USA). A samplesize calculation was not performed for this pilot study. Coagulation tests (INR, APTTr and fibrinogen concentration) were compared using unpaired t-tests, and blood component administration compared using Mann–Whitney U-tests.

Results

Twenty-three patients were assessed for enrolment in the study of whom 20 completed the study (10 in each group) (Fig. 1). Baseline characteristics of participants are shown in Table 2. In each group, nine patients were taking aspirin and this was not omitted before surgery. One patient allocated to FFP was taking dipyridamole in addition to the aspirin, but this was discontinued 5 days

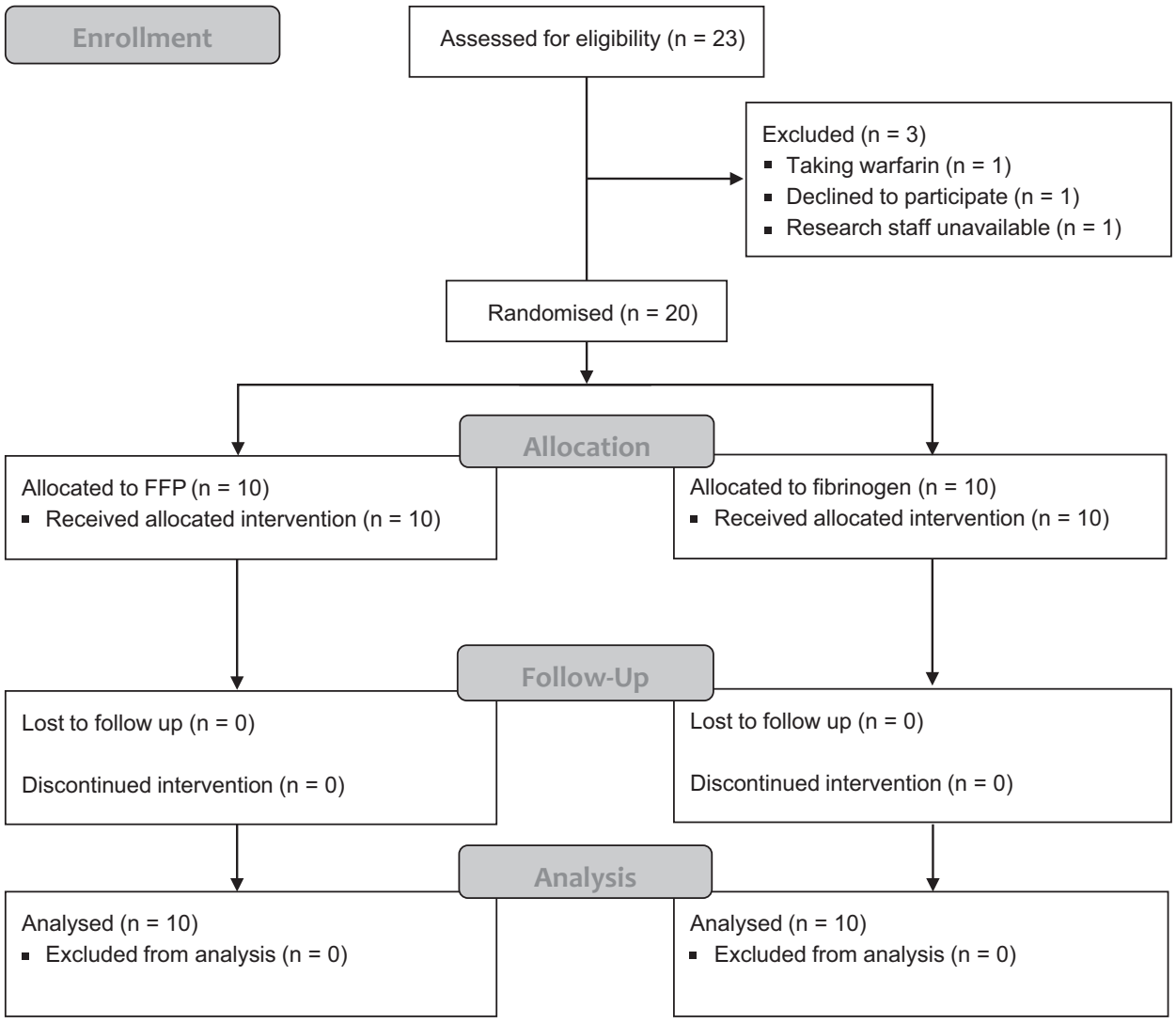

Figure 1 CONSORT flow diagram. FFP, fresh frozen plasma.

Table 2 Baseline characteristics of patients randomly allocated to receive either fresh frozen plasma (FFP) or fibrinogen concentrate during thoraco-abdominal aortic aneurysm surgery. Values are number, mean (SD) or median (IQR [range]).

	FFP n = 10	Fibrinogen n = 10
Sex; male	6	8
Age; years	71.5 (5.9)	71.4 (3.9)
Body mass index; $kg.m^{-2}$	26.7 (5.3)	25.9 (3.3)
RCRI score	1 (1–2[0–2])	1 (1–2[0–3])
Haemoglobin; $g.l^{-1}$	131.0 (12.7)	132.0 (15.8)
Platelet count; x $10^9.l^{-1}$	213 (72)	232 (61)
Plasma fibrinogen concentration; $g.l^{-1}$	3.1 (0.8)	3.7 (0.8)

RCRI, revised cardiac risk index.

before surgery. In addition, one patient in each group (those who were not taking aspirin pre-operatively) received prophylactic dose subcutaneous dalteparin on the evening before surgery.

Intra-operative blood loss and fluid administration volumes are shown in Table 3, with intra-operative blood component and fibrinogen concentrate administration shown in Fig. 2 and Table 4. No FFP was given to the 10 patients allocated to fibrinogen concentrate during surgery. Only two patients allocated to fibrinogen concentrate, with intra-operative blood losses of 9725 ml and 11,800 ml received platelet transfusions during surgery. All patients in both groups were assessed by the surgeon to have satisfactory haemostasis at the end of surgery.

After the end of surgery, but while the patient was still in the operating theatre, one of the patients allocated to fibrinogen concentrate developed signs suggestive of haemorrhage. The abdomen was re-opened and bleeding from a small artery was found requiring surgical correction. On closing the abdomen at the end of the initial operation (total estimated blood loss 7900 ml), the surgeon had assessed haemostasis as normal and the ROTEM trace was satisfactory. The patient received a further seven units of red cells, 8 g of fibrinogen concentrate and one pool of platelets, but no FFP. The total cumulative blood loss for this patient was 12,200 ml. At the end of the re-opening, the surgeon's clinical assessment was that haemostasis was satisfactory but the EXTEM CT result was prolonged beyond the pre-defined trigger for FFP transfusion so the patient received two units of FFP in the operating room. Apart from this case, no other patients had clinical signs suggestive of surgical site bleeding after surgery.

Table 3 Blood loss, returned cell salvage volume and infused crystalloid and colloid volumes in patients randomly allocated to receive either fresh frozen plasma (FFP) or fibrinogen concentrate during thoraco-abdominal aortic aneurysm surgery. Values are mean (SD).

	FFP n = 10	Fibrinogen n = 10
Blood loss; ml	7738 (4277)	6849 (3082)
Returned cell salvage; ml	2399 (1268)	2280 (952)
Hartmann's solution; ml	4705 (1183)	5423 (1552)
4.5% human albumin solution; ml	100 (316)	2100 (1049)
Volulyte; ml	1350 (709)	1500 (408)
Geloplasma; ml	3000 (1054)	2800 (1033)
Total crystalloid/colloid; ml	9155 (1825)	11755 (2995)

Blood component transfusions in the first 24 h after surgery are shown in Table 5. Three patients allocated to fibrinogen concentrate (including the patient described above) received FFP in the critical care unit postoperatively because the APTTr was > 2.0 despite a laboratory fibrinogen concentration in the normal range (intra-operative blood losses 9725 ml, 11,800 ml and 12,200 ml). There were no clinical signs of bleeding in these three patients and each patient received either one or two units of FFP which is less than a standard adult dose. Our protocol specified that FFP should be given if the APTTr was > 2.0 but not how much should be given. In the absence of clinical signs of bleeding, the clinicians looking after the patients in critical care elected to give only one or two units of FFP. Three patients in the fibrinogen group, all with intra-operative blood losses > 9000 ml, received platelets in the first 24 h after surgery.

Median (IQR [range]) total allogeneic blood component administration during surgery and in the first 24 h postoperatively was 22.5 (14–28[2–41]) units in patients allocated to FFP vs. 4.5 (3–11[0–17]) units in patient allocated to fibrinogen concentrate (p = 0.011); this includes the components given during the re-opening operation described above.

Results from blood samples taken 2 h postoperatively showed mean (SD) fibrinogen concentration of 1.6 (0.3) $g.l^{-1}$ in patients allocated to FFP and 1.6 (0.2) $g.l^{-1}$ in patient allocated to fibrinogen concentrate (p = 0.36). At the same time-point, the mean (SD) INR and APTTr were lower in patients allocated to FFP compared with patient allocated to fibrinogen concentrate (1.1 (0.1) vs. 1.8 (0.3); p < 0.0001 and 1.1 (0.2) vs. 1.7 (0.5); p = 0.032, respectively). Mean (SD) platelet counts were similar in both groups (72 (34) × $10^9.l^{-1}$ and 96 (75) × $10^9.l^{-1}$, respectively; p = 0.39).

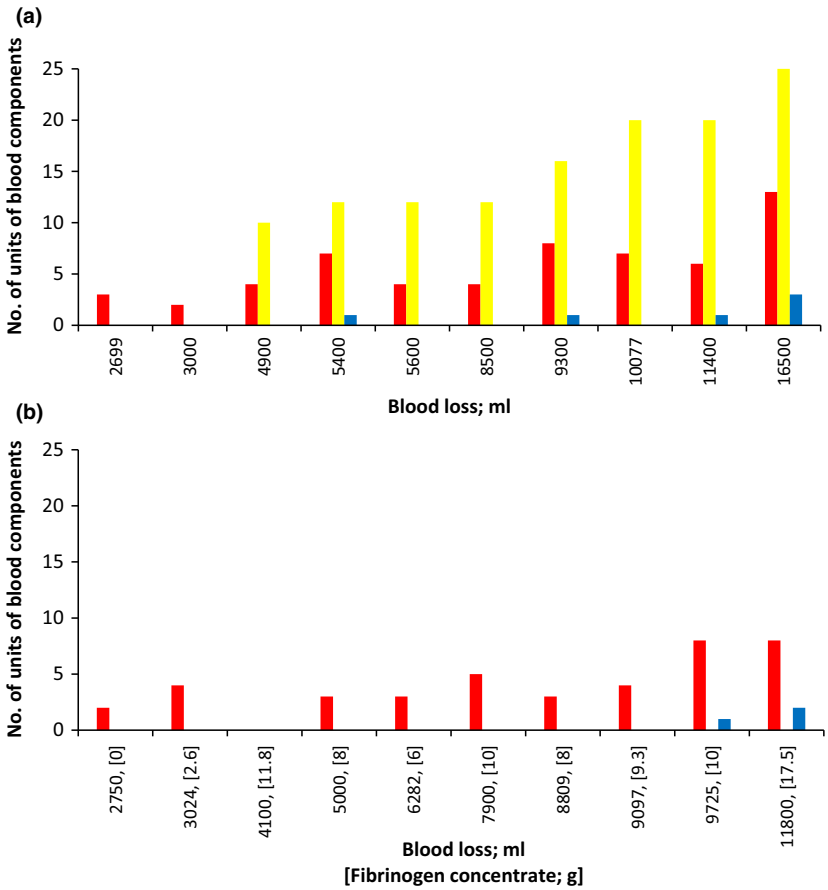

Figure 2 Blood component administration (red = packed red cells, yellow = fresh frozen plasma, blue = platelets) during surgery for each patient randomly allocated to receive either fresh frozen plasma (FFP) (a) or fibrinogen concentrate (b) during thoraco-abdominal aortic aneurysm surgery. Blood loss and fibrinogen concentrate administration during surgery is also shown.

Postoperative complications and duration of stay in critical care and hospital were similar in both groups (Table 6).

Discussion

We used fibrinogen concentrate as an alternative to FFP in the treatment of acquired hypofibrinogenaemia during major vascular surgery. All patients who received fibrinogen concentrate had satisfactory clotting at the end of surgery as assessed by point-of-care testing. Patients who received fibrinogen concentrate and who had a measured blood loss during surgery of up to 8800 ml did not receive any blood component transfusion apart from red cells during surgery or in the first 24 h after surgery.

As this is a pilot study involving a small number of patients, caution should be exercised in the interpretation of these findings. However, our results suggest that when fibrinogen concentrate is given it may be feasible to avoid the transfusion of haemostatic blood components (FFP, cryoprecipitate and platelets) during and after elective major vascular surgery with intra-operative blood loss of up to 9000 ml.

Previous retrospective studies have compared the administration of fibrinogen concentrate and prothrombin complex concentrate (PCC) with the administration of FFP in cardiac surgery [16] and trauma [17]. However, we believe this to be the first study in which an infusion of fibrinogen during surgery has been used to prevent or correct hypofibrinogenaemia.

We maintained or corrected plasma fibrinogen concentration to around 1.5 $g.l^{-1}$, the lower end of the normal reference range because, in our experience, this is usually associated with the absence of visible microvascular bleeding during open thoraco-abdominal aortic aneurysm repair. In previous studies of fibrinogen concentrate, a higher target plasma fibrinogen concentration has often

Table 4 Intra-operative blood component/product administration in patients randomly allocated to receive either fresh frozen plasma (FFP) or fibrinogen concentrate during thoraco-abdominal aortic aneurysm surgery. Values are median (IQR [range]) or number.

	FFP n = 10	Fibrinogen n = 10
PRC; units	5 (4–7 [2–13])	3.5 (3–5 [0–8])
Patients who received PRC during surgery; n	10	9
FFP; units	12 (10–20 [0–25])	–
Patients who received FFP during surgery; n	8	–
Platelets; pools	0 (0–1[0–3])	0 (0–0[0–2])
Patients who received platelets during surgery; n	4	2
Fibrinogen concentrate; g	–	8.5 (6–10[0–17.5])
Patients who received fibrinogen concentrate during surgery; n	–	9

PRC, packed red cells.

Table 5 Total number of blood components administered to patients randomly allocated to receive either fresh frozen plasma (FFP) or fibrinogen concentrate during thoraco-abdominal aortic aneurysm surgery in the first 24 h after surgery.

	FFP n = 10	Fibrinogen n = 10*
Packed red cells	6	3
Fresh frozen plasma	2	5
Platelets	7	2

*The components transfused when a patient was re-opened in the operating room due to arterial bleeding are not included here but are described in the text.

Table 6 Postoperative complications and duration of stay in patients randomly allocated to receive either fresh frozen plasma (FFP) or fibrinogen concentrate during thoraco-abdominal aortic aneurysm surgery. Values are number or median (IQR [range]).

	FFP n = 10	Fibrinogen n = 10
Myocardial infarction	1	1
Arrhythmia	3	1
Stroke	–	–
Pulmonary embolus	1	–
Renal replacement therapy	1	–
Lower limb weakness	1 [epidural haematoma]	1 [spinal cord ischaemia]
Need for lung ventilation	3	2
Critical care duration of stay; days	4 (3–7 [3–22])	4 (3–9 [3–32])
Hospital duration of stay; days	16.5 (10–19 [8–28])	15 (8–24 [7–53])
30-day mortality; n	1 [perforated duodenal ulcer]	–

been used. Studies using thromboelastometry results as the end-point suggest that a higher fibrinogen concentration may further improve haemostasis [18] and partially compensate for the effect of a low platelet count on clot strength [19]. However, the clinical benefits of raising the plasma fibrinogen concentration above the lower end of the normal range are less certain. In a trial of patients having open aortic surgery who were bleeding after the end of cardiopulmonary bypass, the administration of fibrinogen concentrate (which raised the median plasma fibrinogen concentration from approximately 1.8 $g.l^{-1}$ to 3.0 $g.l^{-1}$) did not reduce blood loss or transfusion requirements [20]. Similarly, in a study of patients having high-risk cardiac surgery who were bleeding after the end of bypass and had a mean fibrinogen concentration of 1.7 $g.l^{-1}$, the administration of fibrinogen concentrate did not reduce subsequent intra-operative blood loss [21]. A study of patients with postpartum haemorrhage concluded that fibrinogen replacement is not required if the plasma fibrinogen concentration is > 2 $g.l^{-1}$, but a beneficial effect below that level could not be excluded [22]. On the other hand, a study of fibrinogen concentrate administration after complex cardiac surgery to patients with risk factors for transfusion whose fibrinogen concentrations appear, in most cases, to have been > 1.5 $g.l^{-1}$ resulted in a reduction in blood component transfusion and postoperative bleeding [23, 24]. The same group, after a larger but retrospective study [25], proposed 1.15 $g.l^{-1}$ as a trigger value for fibrinogen supplementation after cardiac surgery with a post-treatment target value of 2.80 $g.l^{-1}$. In actively bleeding patients, these values were increased to 2.15 $g.l^{-1}$

and 3.75 $g.l^{-1}$, respectively. However, no patient included in this retrospective study was actually treated with fibrinogen concentrate or cryoprecipitate.

The Association of Anaesthetists guidelines on the use of blood components and their alternatives recommend the administration of cryoprecipitate as a source of fibrinogen if the plasma fibrinogen concentration is < 1.5 $g.l^{-1}$ in a bleeding patient [26]. However, cryoprecipitate is thought to carry a higher risk of complications than fibrinogen concentrate [11] and for that reason is no longer available in many European countries. The British Society of Haematology guideline for the diagnosis and management of the rare coagulation disorders recommends that: "*If available, specific recombinant or virally inactivated plasma-derived factor concentrates should be used in preference to FFP or cryoprecipitate*" [27]. To this end, virally inactivated plasma-derived fibrinogen concentrate is usually used rather than cryoprecipitate for the treatment of congenital fibrinogen deficiency. However, in the UK, the use of fibrinogen concentrate for acquired fibrinogen deficiency, as occurs in surgical and obstetric haemorrhage and trauma, is complicated by the fact that the marketing authorisation only lists "*Treatment of bleeding in patients with congenital hypo-, or afibrinogenaemia with bleeding tendency*" as an indication, so that its use in other circumstances is 'off-label'. Cryoprecipitate, on the other hand, is exempt from the requirement to have a marketing authorisation because, not having undergone purification and processing steps such as those undertaken to produce a factor concentrate, it is not classified as a medicinal product.

Fresh frozen plasma is commonly used as the first-line blood component therapy for impaired coagulation in bleeding surgical, trauma and obstetric patients as a source of coagulation factors. Guidelines typically recommend its administration when the INR or APTTr is > 1.5. However, in major haemorrhage in surgery [5], obstetrics [28] and trauma [29], low fibrinogen concentration is usually the first deficiency to result in impaired haemostasis, and hypofibrinogenaemia may itself lead to a prolonged INR and APTTr since the end-point of these tests is the formation of fibrin. A standard adult therapeutic dose of FFP contains approximately 2.8 g of fibrinogen [12, 13]. Therefore, it may well be that the principal benefit of FFP administration to these patients is the correction of hypofibrinogenaemia. Although fibrinogen concentrate has usually been considered to be an alternative to the use of cryoprecipitate in bleeding surgical, obstetric and trauma patients, we suggest that it should also be considered an alternative to FFP.

Mathematical modelling demonstrates that fibrinogen concentrate (or cryoprecipitate) can raise plasma fibrinogen concentration to a greater extent than FFP because the fibrinogen is delivered in a more concentrated form [30]. This is indeed the case if no additional i.v. fluid is given other than the fibrinogen concentrate or cryoprecipitate. However, in the case of major haemorrhage as in the present study, the volume of other i.v. fluids required to restore and maintain circulating volume is likely to be greater when fibrinogen concentrate or cryoprecipitate is used rather than FFP and this may reduce or abolish the effect of giving a more concentrated source of fibrinogen.

Since FFP contains both fibrinogen and other coagulation factors, and fibrinogen concentrate contains only fibrinogen in significant quantities, a concern was that patients in the fibrinogen group would develop a clinically significant coagulopathy due to low concentrations of other coagulation factors. There was indeed a significant difference between the postoperative INR and APTTr between the two groups, consistent with the lower concentrations of coagulation factors other than fibrinogen that would be expected in the fibrinogen group. However, in these patients, the elevated INR and APTTr values in combination with normal fibrinogen concentration results were not associated with clinical signs of bleeding. It is not clear at what level treatment is required for an elevated postoperative INR or APTTr value in this situation. In patients bleeding during or after surgery, prolonged INR or APTTr results may be associated with, or indeed caused by, hypofibrinogenaemia and the clinical significance of prolonged INR and APTTr may be different in patients in whom hypofibrinogenaemia has been prevented or corrected. If it is considered appropriate to correct the deficiency of coagulation factors other than fibrinogen, this may be achieved either by giving FFP or PCC. We had pre-defined ROTEM and laboratory result triggers for giving additional coagulation factors in the form of FFP which resulted in three of the patients in the fibrinogen group receiving FFP after surgery.

The use of fibrinogen concentrate rather than FFP or cryoprecipitate has advantages in terms of a reduced risk of immunological complications and probably of infection transmission and in the ease and speed of acquisition and administration, avoiding the logistical difficulties with the transport, storage, compatibility testing and issue of frozen blood components. On the other hand, FFP administration will increase the concentration of other coagulation factors and may have a protective effect on the endothelial glycocalyx [31]. Current guidelines on the management of

bleeding surgical, trauma and obstetric patients [27, 32, 33] recommend maintaining a fibrinogen concentration of 1.5 $g.l^{-1}$ or 2.0 $g.l^{-1}$. A comparison of the effect on mortality and morbidity of a management strategy for major haemorrhage based on giving fibrinogen concentrate to achieve this level vs. one based on transfusing blood components requires a larger randomised study powered to detect differences in clinical outcomes. This question remains unanswered because recent studies of fibrinogen concentrate have sought to answer a different question, that is, whether it is beneficial to give additional fibrinogen to patients whose plasma fibrinogen concentration already exceeds 1.5 $g.l^{-1}$ or 2.0 $g.l^{-1}$.

There are some limitations to our study. First, this was a pilot study that was not powered to detect differences in clinical outcomes. Second, the clinicians caring for the patients were not blinded to the treatment group. However, the decision as to whether to administer a blood component transfusion was made on the basis of pre-defined ROTEM and laboratory test transfusion triggers and it is unlikely that blinding would have resulted in additional transfusions. Third, large volumes of synthetic colloid fluids were given to both groups as was our routine practice at the time of the study, and this may have impaired coagulation [7, 8]. Our current practice is to use predominantly crystalloid fluids with a much lower volume of colloids and it is possible that with this approach the impairment of haemostasis and need for haemostatic blood component transfusions may be further reduced.

This study suggests that fibrinogen concentrate may be given instead of FFP to treat coagulopathy during complex vascular surgery and that its use results in reduced allogeneic blood component transfusion. A larger study is required to establish whether the administration of fibrinogen concentrate rather than FFP during surgery leads to a difference in clinical outcomes.

Acknowledgements and competing interests

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