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ORIGINAL RESEARCH

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Comparison of coagulation parameters associated with fibrinogen concentrate and cryoprecipitate for treatment of bleeding in patients undergoing cytoreductive surgery for pseudomyxoma peritonei: Subanalysis from a randomized, controlled phase 2 study

Ashok Roy[1] | Nigel Sargant[1] | John Bell[1] | Sophia Stanford[1] | Cristina Solomon[2] | Irina Kruzhkova[2] | Sigurd Knaub[2] | Faheez Mohamed[1]

[1]Peritoneal Malignancy Institute, Basingstoke and North Hampshire Hospital, Hampshire, UK

[2]Octapharma AG, Lachen, Switzerland

Correspondence
Faheez Mohamed, Basingstoke and North Hampshire Hospital, Aldermaston Rd, Basingstoke, Hampshire, RG24 9NA, UK.
Email: faheez.mohamed@hhft.nhs.uk

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Octapharma AG

Abstract

Background and Aims: The FORMA-05 study compared the efficacy and safety of human fibrinogen concentrate (HFC) versus cryoprecipitate for hemostasis in bleeding patients undergoing cytoreductive surgery for pseudomyxoma peritonei (PMP). This subanalysis explores coagulation parameters in the FORMA-05 patients, with a focus on the seven patients who developed thromboembolic events (TEEs).

Methods: FORMA-05 was a prospective, randomized, controlled phase 2 study in which patients with predicted blood loss ≥2 L received HFC (4 g) or cryoprecipitate (two pools of five units), repeated as needed. Plasma fibrinogen, platelet count, factor (F) XIII, FVIII, von Willebrand Factor (VWF) antigen and ristocetin cofactor activity levels, EXTEM A20, FIBTEM A20, and endogenous thrombin potential (ETP) were measured perioperatively.

Results: Fibrinogen, platelet count, EXTEM and FIBTEM A20, FXIII, FVIII, VWF levels, and ETP were maintained throughout surgery in both the HFC group ($N = 21$) and the cryoprecipitate group ($N = 23$). Seven TEEs were observed in the cryoprecipitate group. The two patients developing deep vein thromboses (DVT) appeared to have a procoagulant status preoperatively, with distinctively higher fibrinogen level, FIBTEM A20, and platelet levels, all of which persisted perioperatively. The five patients developing pulmonary embolism (PE) had slightly higher VWF levels preoperatively, with a disproportionate increase intraoperatively (postcryoprecipitate administration) and postoperatively.

Conclusions: Patients treated with HFC versus cryoprecipitate showed broad overlaps in coagulation parameters. Patients with PE experienced a disproportionate VWF rise following cryoprecipitate administration, whereas patients developing

DVT displayed a procoagulant status before and following surgery. Preoperative testing may allow these patients to be identified.

KEYWORDS

blood coagulation factor, cytoreduction surgical procedures, fibrinogen, hemorrhage, pseudomyxoma peritonei, venous thrombosis

1 | INTRODUCTION

Pseudomyxoma peritonei (PMP) is a rare malignant growth in the abdomen and pelvis, which has an estimated incidence of two to three per million per year.[1,2] The current state-of-the-art surgical intervention for PMP is the Sugarbaker procedure, which is prolonged and associated with massive surgical blood loss,[3,4] requiring support with allogeneic blood products.[5–7] Coagulopathy during this procedure is predominantly characterized by reduced fibrinogen levels and impaired fibrinogen polymerization, which result in reduced clot firmness.[8,9]

During surgery for PMP, cryoprecipitate has been historically used as fibrinogen replacement therapy, which contains plasma proteins including fibrinogen, factor VIII (FVIII), factor XIII (FXIII), and von Willebrand factor (VWF).[10] As cryoprecipitate is prepared from plasma, the fibrinogen and plasma protein concentrations are not standardized and vary between batches.[11] Furthermore, cryoprecipitate can contain impurities such as platelet microparticles and fibronectin. The effect of these impurities and plasma proteins is unclear; however, they may contribute to thrombotic risk.[12] Cryoprecipitate must be stored frozen, requiring time to thaw and blood group match before transfusion. Cryoprecipitate is also associated with risks of transfusion-related acute lung injury and pathogen transmission.[10,13]

An alternative source of fibrinogen is purified human fibrinogen concentrate (HFC). HFC undergoes virus inactivation and has rapid preparation times, as it does not require blood group matching or thawing, making it potentially safer and logistically advantageous.[12] Furthermore, the defined fibrinogen content allows accurate and standardized dosing, with fewer extraneous proteins and smaller infusion volumes.[11] The use of HFC to correct acquired fibrinogen deficiency (hypofibrinogenemia) has been described in various clinical settings, including surgery, trauma, and major obstetric hemorrhage.[14–17] Plasma-derived HFC was shown to be noninferior to cryoprecipitate in terms of efficacy and its safety profile was shown to be favorable compared with cryoprecipitate in a large randomized clinical trial of cardiac surgery patients with acquired fibrinogen deficiency.[18] However, data concerning changes in coagulation parameters following administration of purified HFC versus cryoprecipitate in bleeding patients is limited, in particular regarding differences in levels of coagulation parameters due to the additional factors present in cryoprecipitate versus HFC.

The prospective, randomized FORMA-05 study[19] showed that purified HFC (*Fibryga*®, Octapharma AG) maintained overall hemostatic efficacy in bleeding patients with acquired fibrinogen deficiency undergoing surgery for PMP, with a posthoc analysis demonstrating noninferiority to cryoprecipitate. Seven thromboembolic events (TEEs) were reported in the study, all of which occurred in patients treated with cryoprecipitate. Unlike congenital afibrinogenemia, which is associated with thromboembolic complications

Key points

What's known

- Purified human fibrinogen concentrate (HFC) has been used for fibrinogen replacement in acquired bleeding across a number of clinical settings including surgery, trauma and major obstetric hemorrhage. The randomized, controlled, FORMA-05 study compared efficacy and safety of HFC and cryoprecipitate for hemostasis in surgical bleeding during major abdominal surgery. HFC maintained overall hemostatic efficacy with noninferiority to cryoprecipitate, with coagulation factor levels maintained throughout surgery.

What's new

- This subanalysis of the FORMA-05 study examined the changes in coagulation parameters during and after surgery in patients receiving HFC versus cryoprecipitate. Seven patients experienced thromboembolic events (TEEs), all of whom were on cryoprecipitate. Of these, two patients had deep vein thromboses (DVT), with higher fibrinogen, FIBTEM A20, and platelet levels, which persisted perioperatively. The five patients who developed pulmonary embolism (PE) had slightly higher preoperative von Willebrand factor (VWF) levels, which increased disproportionately following cryoprecipitate administration and postoperatively.

Clinical implications

- Study results indicated a procoagulant status in patients experiencing DVT, and a disproportionate intra- and postoperative increase in VWF for patients experiencing PE. Larger studies in more diverse surgical settings should consider recording coagulation factor levels to gain a better understanding of how coagulation factor levels relate to TEEs.

both with and without treatment,[20] no evidence is available on the likelihood of TEEs following the use of fibrinogen replacement therapy in acquired fibrinogen deficiency.[21]

The primary analysis from FORMA-05 showed that levels of FXIII, FVIII, and VWF activity were maintained throughout surgery, and noted that analysis of coagulation parameters would be described in more detail in a separate publication. This manuscript presents the results of this posthoc analysis envisaged at the time of the primary analysis, which aimed to determine if there were any differences in other coagulation parameters during and after surgery for PMP, in patients who received HFC versus those who received cryoprecipitate. In particular, aims of this analysis were to establish whether there were any specific changes in coagulation parameters in patients who experienced TEEs during the study.

2 | MATERIALS AND METHODS

The FORMA-05 study was a single-center, prospective, randomized, controlled phase 2 study in adult patients undergoing cytoreductive surgery (CRS) surgery for PMP, as described previously.[19] The study was approved by the National Health Service Health Research Authority, South Central–Hampshire A Research Ethics Committee in the United Kingdom (Ref: 16/SC/0576) and was conducted in accordance with the Declaration of Helsinki. Patients provided voluntary, written informed consent before participating.

At ~90 min into the surgery when the abdominal cavity was open and the extent of the surgery could be thoroughly assessed, patients were randomized to receive HFC (4 g) or cryoprecipitate (two pools of five units; ~4.0–4.6 g fibrinogen) if average intraoperative blood loss in the absence of targeted fibrinogen replacement was predicted to be ≥2 L. Further administration of HFC or cryoprecipitate intraoperatively was based on the ROTEM FIBTEM A20 test, whereas postoperative doses were based on clinical judgment guided by the FIBTEM A20 test, as described previously.[19]

Plasma fibrinogen levels were measured using the Clauss assay preoperatively (baseline), every hour during surgery, at the end-of-surgery, and at 6, 12, 24, and 48 h and on Day 10 after surgery. The contribution of fibrin to clot strength was also assessed at these timepoints using the ROTEM FIBTEM A20 test. The following coagulation parameter plasma levels were measured preoperatively (baseline), every 2 h during surgery, and at 6, 12, 24, and 48 h, and 10 days after surgery: FVIII activity (FVIII:C), FXIII, and VWF as measured by ristocetin cofactor activity [VWF:RCo] and VWF antigen, and platelet count, as well as endogenous thrombin potential (ETP).

Statistical analyses and sample size calculations for the FORMA-05 study were performed as described previously.[19] In this posthoc analysis, descriptive statistics were used to explore changes in coagulation factors over time in patients with and without TEE occurrence during the study. Coagulation factor changes were explored in patient groups and subgroups as follows: all patients who received HFC (none of whom experienced TEEs); all patients who received cryoprecipitate; patients who experienced pulmonary embolism (PE); patients who experienced deep vein thrombosis (DVT); and patients who received cryoprecipitate who did not experience any TEEs.

3 | RESULTS

3.1 | Study population

The FORMA-05 study full analysis set included 45 patients aged 18 years or older. The median (range) age was 61 years (34–76), with 25/45 (55.6%) patients being female and 44/45 (97.8%) patients classified as White race, with one patient classified as Asian. The mean (±SD) peritoneal cancer index total score was 28 (±8), and the median (range) was 30.00 (7–39). The characteristics of this population have been described previously, with no statistically significant differences between demographic parameters observed between the HFC and cryoprecipitate groups and with similar risk factors for thrombosis in both treatment arms.[19]

3.2 | Adverse events

Overall, seven TEEs were reported during the study, all of which occurred in patients who received cryoprecipitate (Table 1).

Two instances of DVT were reported, both identified during Day 10 routine Doppler examinations and classified as serious adverse events (SAEs). The severity of both events was assessed as “mild.” Both patients who developed DVT received a single intraoperative infusion of two pools of five units cryoprecipitate around 2 h after surgery start. One patient had ongoing hypertension and increased blood cholesterol, whereas the other had aortic valve incompetence and epilepsy, with a past cardiac operation for heart valve replacement and atrioventricular block with a pacemaker in 2003.

Five patients who had received cryoprecipitate each experienced one instance of PE, all of which were identified between 4 and 8 days following surgery by CT pulmonary angiogram and classified as SAEs. The severity of each of these events was assessed as “moderate.” All patients who developed PE received a single intraoperative cryoprecipitate infusion around 2 h after surgery start, with two patients requiring one further intraoperative dose and one patient requiring two further intraoperative doses (all doses were two pools of five units). Of these five patients, two were reported as having no relevant medical history. One patient had a history of hypertension, asthma, psoriatic arthritis, and ankylosing spondylitis and glaucoma in anamnesis, and one patient had a history of psoriasis and colitis with a sebaceous cyst previously excised from the chest and laparoscopy for a planned appendectomy. The fifth patient had a medical history of rheumatoid arthritis, nephrolithiasis, angina pectoris, and hypertension with a coronary artery bypass graft performed in 2009. Three days following the identification of PE, the patient developed sudden shortness of breath and increased oxygen requirement with left

TABLE 1 Medical details of all TEEs reported in FORMA-05.

Treatment group	Patient age (years) and gender (M/F)	BMI (kg/m^2)	Event	Tumor grading	Event details	Outcome	Causality
Cryoprecipitate	65 F	36.27	DVT	Low-grade appendiceal mucinous neoplasm	Day 10 routine Doppler identified isolated right and left calf DVT. The patient was asymptomatic with no relevant medical history. Event classified as SAE. The severity of the event was classified as "mild."	Recovering, resolving	Unlikely related
Cryoprecipitate	67 M	27.17	DVT	Signet ring cell adenocarcinoma	Day 10 routine Doppler identified right and left calf DVT. Patient was asymptomatic, with a medical history of aortic regurgitation, open-heart surgery, complete heart block, pacemaker and porcine valve since 2003. Event classified as SAE. The severity of the event was classified as "mild."	Recovering, resolving	Unlikely related
Cryoprecipitate	46 M	24.90	PE	Low-grade appendiceal mucinous neoplasm	Oxygen saturation was 90% 7 days after surgery. Reduced breath sounds were noticed over both lung bases. CTPA showed multiple filling defects affecting the right lower lobe and the right middle lobe arteries. Event classified as SAE. The severity of the event was classified as "moderate."	Recovering, resolving	Unlikely related
Cryoprecipitate	50 F	40.14	PE	Low-grade appendiceal mucinous neoplasm	Oxygen saturation was 86% 3 days after surgery. PE was diagnosed 4 days after surgery. CTPA showed bilateral multiple PEs. No relevant medical history was identified. Event classified as SAE. The severity of the event was classified as "moderate."	Recovering, resolving	Unlikely related
Cryoprecipitate	66 M	32.39	PE	Low-grade appendiceal mucinous neoplasm	Oxygen saturation was 90% on 4 L/min oxygen 7 days after surgery. CTPA confirmed bilateral PE 8 days after surgery. Event classified as SAE. The severity of the event was classified as "moderate."	Recovering, resolving	Unlikely related
Cryoprecipitate	72 M	24.21	PE	Low-grade appendiceal mucinous neoplasm	Patient had pain in chest area 8 days after surgery. CTPA confirmed small peripheral thrombus in pulmonary anterior branch and left upper lobe. Patient was given IV dose of high molecular weight heparin. Event classified as SAE. The severity of the event was classified as "moderate."	Recovering, resolving	Unlikely related
Cryoprecipitate	61 M	28.91	PE	Low-grade appendiceal mucinous neoplasm	Tachycardia with first-degree heart block was diagnosed 6 days after surgery. A bilateral CTPA identified pleural effusions and equivocal PE. CT scan identified abdominal collection. Event classified as SAE. The severity of the event was classified as "moderate."	Recovering, resolving	Unlikely related

Abbreviations: BMI, body mass index; CT, computed tomography; CTPA, computed tomography pulmonary angiography; DVT, deep vein thrombosis; F, female; M, male; PE, pulmonary embolism; SAE, serious adverse event; TEE, thromboembolic event.

pleural effusion revealed by chest X-ray. One day later, the patient was diagnosed with gastric leakage with large contamination, which was treated with emergency laparotomy. The patient's condition continued to deteriorate, with death occurring 2 days later.

All seven patients who experienced a TEE were treated daily with enoxaparin and all TEEs given a final outcome of recovering and resolving. As the PE events start date was between 4 and 8 days following surgery (beyond the half-life of the administered coagulation factors that may be seen as risk factors for thrombosis), and the start of the DVTs was at the Day 10 follow-up with evidence lacking for a different relatedness evaluation, all TEEs reported in this study were assessed by the study investigator as unlikely to be related to the study treatment.

3.3 | Coagulation parameters

We previously showed that levels of FXIII, FVIII, and VWF activity, as well as EXTEM and FIBTEM A20, were sufficiently maintained during surgery in patients in both the HFC and cryoprecipitate groups (indicated here in Figures 1 and 2 in blue and green, and Table 2).[19] As shown previously,[19] there were significantly greater mean increases with HFC in plasma fibrinogen and FIBTEM A20 levels than with cryoprecipitate. Two hours after surgery start, throughout the remaining intraoperative period and postoperative timepoints, plasma fibrinogen and FIBTEM A20 were numerically higher in the HFC group than in the cryoprecipitate group. The current analysis additionally shows that levels of VWF antigen, ETP, and platelet

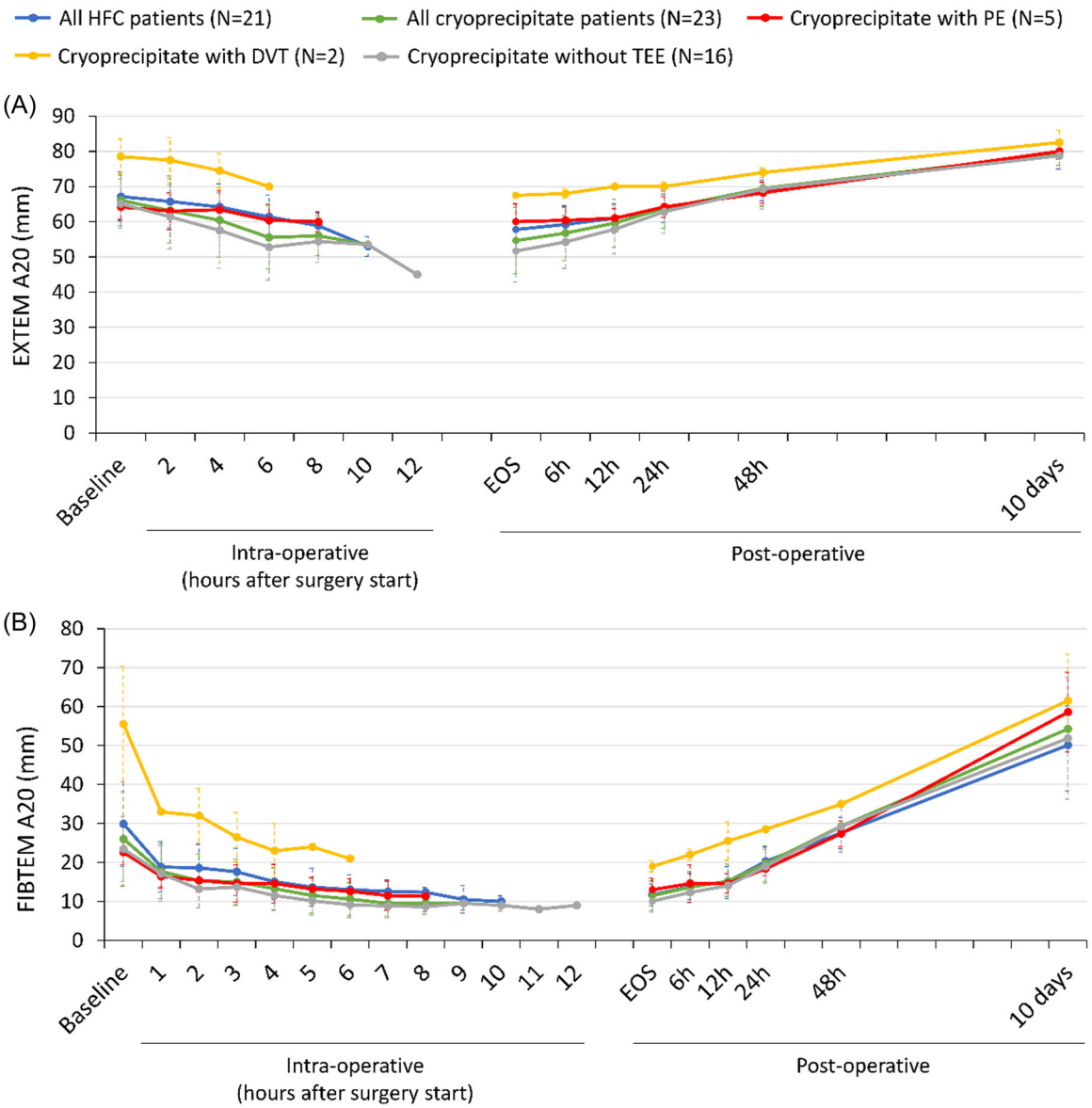

FIGURE 1 Intra- and postoperative changes in ROTEM parameters. (A) EXTEM A20 and (B) FIBTEM A20, stratified by occurrence or absence of TEEs. DVT, deep vein thrombosis; EOS, end of surgery; PE, pulmonary embolism; TEE, thromboembolic event. All values presented are mean values with the error bars representing SD.

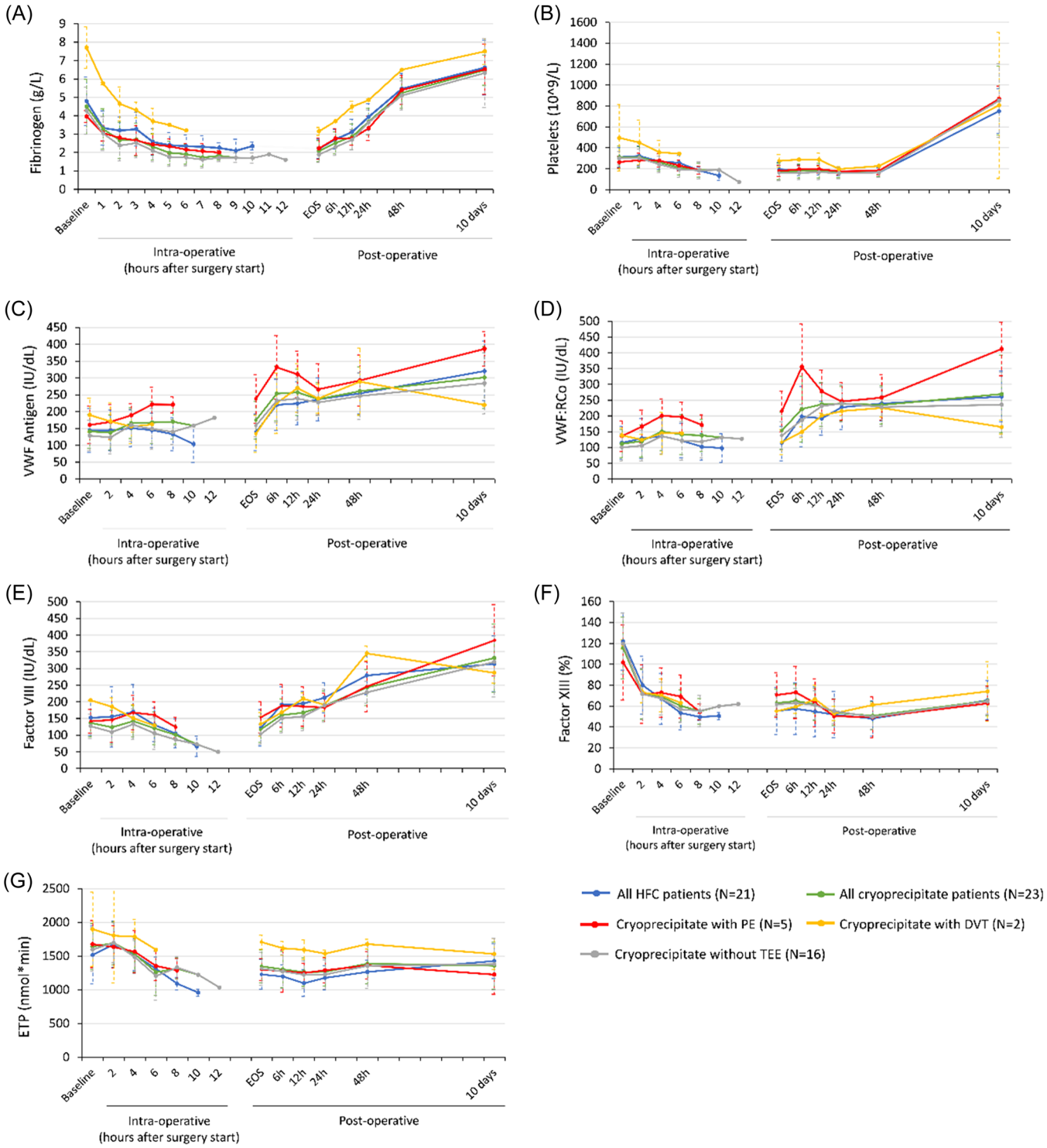

FIGURE 2 Intra- and postoperative changes in (A) plasma fibrinogen levels, (B) platelet count, (C) von Willebrand factor (VWF) antigen, (D) VWF ristocetin cofactor (VWF:RCo) activity, (E) factor VIII (FVIII), (F) factor XIII (FXIII), and (G) endogenous thrombin potential, stratified by occurrence or absence of TEEs. DVT, deep vein thrombosis; EOS, end of surgery; PE, pulmonary embolism; TEE, thromboembolic event. All values presented are mean values with the error bars representing SD.

count were maintained intra- and postoperatively in both the HFC and cryoprecipitate groups (Figure 2).

This posthoc analysis also examined the coagulation parameter profiles of patients who experienced DVT or PE compared with those who did not experience TEEs. Of note, the two patients in the cryoprecipitate group who experienced DVT had a distinctively higher procoagulation status before surgery, as indicated by FIBTEM A20 (136.8% than patients with no TEEs in the cryoprecipitate group

TABLE 2 Coagulation parameters of patients undergoing surgery in FORMA-05, mean (SD).

		Cryoprecipitate			
	HFC (*N* = 21)	Experienced DVT (*N* = 2)	Experienced PE (*N* = 5)	No TEE (*N* = 16)	All (*N* = 23)
Fibrinogen concentration (g/L)					
Baseline	4.8 (1.3)	7.7 (1.1)	4.0 (0.3)	4.3 (1.3)	4.5 (1.5)
2 h intraoperative	3.2 (0.7)	4.7 (0.9)	2.8 (0.4)	2.4 (0.8)	2.7 (1.0)
4 h intraoperative	2.6 (0.7)	3.7 (0.7)	2.4 (0.6)	2.1 (0.6)	2.3 (0.7)
6 h intraoperative	2.3 (0.6)	3.2 (N/A)	2.2 (0.3)	1.7 (0.5)	1.9 (0.5)
6 h postoperative	2.7 (0.5)	3.7 (0.0)	2.8 (0.5)	2.3 (0.4)	2.5 (0.6)
24 h postoperative	3.9 (0.7)	4.9 (0.1)	3.3 (0.7)	3.6 (0.7)	3.7 (0.7)
10 days postoperative	6.6 (1.5)	7.5 (0.7)	6.5 (1.4)	6.3 (1.9)	6.5 (0.8)
FIBTEM A20 (mm)					
Baseline	29.9 (10.9)	55.5 (14.8)	22.6 (3.2)	23.4 (8.4)	26.0 (12.1)
2 h intraoperative	18.6 (6.1)	32.0 (7.1)	15.4 (2.9)	13.2 (4.8)	15.3 (6.9)
4 h intraoperative	15.0 (4.5)	23.0 (7.1)	14.6 (4.7)	11.5 (3.9)	13.3 (5.4)
6 h intraoperative	13.1 (3.8)	21.0 (N/A)	12.6 (3.2)	9.1 (3.3)	10.6 (4.2)
6 h postoperative	13.8 (3.4)	22.0 (1.4)	14.6 (4.7)	12.3 (2.7)	13.7 (4.1)
24 h postoperative	20.3 (3.7)	28.5 (0.7)	18.4 (1.8)	19.0 (4.4)	19.7 (4.6)
10 days postoperative	50.1 (11.7)	61.5 (12.0)	58.6 (10.3)	51.9 (15.6)	54.3 (5.9)
VWF antigen (IU/dL)					
Baseline	144.4 (65.6)	190.1 (50.0)	160.3 (55.4)	128.8 (44.9)	141.0 (49.6)
2 h intraoperative	144.1 (61.1)	170.8 (55.4)	169.6 (52.1)	123.4 (48.6)	137.6 (52.2)
4 h intraoperative	150.7 (54.5)	155.4 (51.2)	189.2 (34.5)	159.6 (48.6)	165.7 (45.9)
6 h intraoperative	145.0 (51.0)	162.0 (N/A)	221.4 (51.1)	148.7 (60.6)	167.6 (62.6)
6 h postoperative	220.1 (76.3)	225.4 (89.6)	331.7 (93.9)	232.7 (65.7)	253.6 (81.8)
24 h postoperative	236.6 (63.2)	238.6 (43.8)	266.1 (76.2)	227.3 (37.5)	237.2 (49.0)
10 days postoperative	320.4 (88.3)	219.5 (3.8)	386.3 (51.8)	284.2 (91.0)	301.5 (92.7)
VWF RCo (IU/dL)					
Baseline	114.8 (52.1)	138.1 (23.5)	136.2 (48.3)	100.2 (43.0)	111.3 (44.8)
2 h intraoperative	128.7 (63.7)	124.5 (18.0)	166.1 (51.5)	105.8 (48.1)	120.5 (52.0)
4 h intraoperative	135.6 (55.5)	144.8 (66.1)	200.7 (53.7)	135.8 (56.9)	150.7 (60.6)
6 h intraoperative	121.8 (55.1)	145.0 (N/A)	196.4 (47.8)	121.0 (61.8)	141.0 (64.0)
6 h postoperative	198.0 (95.3)	149.0 (16.6)	355.3 (135.6)	186.9 (50.0)	221.7 (103.9)
24 h postoperative	227.5 (70.2)	215.6 (13.9)	245.8 (60.1)	240.0 (59.0)	238.8 (55.6)
10 days postoperative	261.4 (80.3)	164.7 (22.1)	412.4 (85.4)	235.5 (103.3)	269.3 (123.6)
FVIII (IU/dL)					
Baseline	152.2 (53.6)	204.5 (1.1)	141.7 (36.1)	126.7 (37.1)	136.7 (40.9)
2 h intraoperative	155.5 (90.6)	184.9 (27.6)	145.5 (66.9)	109.1 (40.4)	123.6 (50.7)
4 h intraoperative	169.7 (81.7)	150.7 (40.9)	167.6 (51.7)	132.8 (45.7)	141.9 (46.9)
6 h intraoperative	130.7 (50.1)	129.0 (N/A)	160.5 (38.9)	105.8 (49.0)	120.6 (48.4)
6 h postoperative	190.7 (54.5)	168.5 (22.5)	188.2 (64.0)	150.5 (44.1)	160.3 (48.4)

(Continues)

TABLE 2 (Continued)

	HFC (*N* = 21)	Cryoprecipitate			
		Experienced DVT (*N* = 2)	Experienced PE (*N* = 5)	No TEE (*N* = 16)	All (*N* = 23)
24 h postoperative	212.2 (45.4)	191.1 (19.7)	182.8 (42.5)	189.1 (48.9)	187.8 (44.3)
10 days postoperative	313.9 (84.2)	286.9 (31.0)	384.1 (106.7)	319.5 (104.5)	331.2 (102.2)
FXIII (%)					
Baseline	121.9 (27.3)	119.0 (4.2)	101.6 (35.7)	119.5 (29.2)	115.6 (29.5)
2 h intraoperative	80.1 (27.6)	73.0 (9.9)	71.6 (27.9)	71.5 (24.6)	71.6 (23.6)
4 h intraoperative	66.9 (24.4)	70.2 (15.8)	72.8 (23.7)	67.2 (15.9)	68.7 (17.1)
6 h intraoperative	53.3 (16.2)	63.0 (N/A)	69.1 (20.5)	57.0 (12.5)	60.3 (15.3)
6 h postoperative	57.3 (24.6)	59.5 (6.3)	73.0 (24.8)	62.9 (13.8)	64.8 (16.3)
24 h postoperative	51.8 (22.1)	53.0 (7.1)	50.4 (15.9)	55.2 (12.3)	53.9 (12.5)
10 days postoperative	65.5 (18.6)	74.0 (28.3)	62.6 (16.2)	64.6 (12.7)	65.0 (14.3)

Abbreviations: DVT, deep vein thrombosis; FVIII, factor VIII; FXIII, factor XIII; HFC, human fibrinogen concentrate; N/A, not available; PE, pulmonary embolism; RCo, ristocetin cofactor; TEE, thromboembolic event; VWF, von Willebrand factor.

and 85.6% higher patients in the HFC group, respectively), plasma fibrinogen levels (80.4% and 60.7% higher, respectively), and platelet count (65.4% and 59.7% higher, respectively). Slightly increased values in the parameters evaluating the overall clot firmness and overall thrombin generation potential were also noted, with mean EXTEM A20 20.5% and 16.9% higher than patients with no TEEs in the cryoprecipitate group and patients in the HFC group, respectively, and mean ETP 18.9% and 25.2% higher, respectively. Increased levels of these parameters persisted both intra- and postoperatively (Figures 1 and 2; see yellow lines).

No differences were seen in the levels of FXIII and FVIII between the HFC and cryoprecipitate groups, or between patients who experienced DVT and those who did not (Figure 2).

The five patients who developed PE had similar EXTEM A20, FIBTEM A20, and levels of plasma fibrinogen, platelets, FVIII:C and FXIII, plus ETP, as compared with patients on cryoprecipitate who did not experience TEEs and patients on HFC. However, these patients exhibited higher VWF antigen and VWF:RCo activity levels both intra- and postoperatively, compared with all other patient groups and subgroups (Figure 2; see red lines). Patients who developed PE had VWF:RCo activity levels 44.2% higher than baseline at 6 h after surgery start and 203% higher than baseline at 10 days postsurgery. When comparing between groups and subgroups for the same timepoints, patients who developed PE had VWF:RCo activity levels 35.9% and 18.6% higher at baseline, 57.0% and 29.1% higher at 2 h after surgery start, 47.8% and 48.0% higher at 4 h after surgery start, 62.3% and 61.3% higher at 6 h after surgery start, 90.1% and 79.4% higher at 6 h postsurgery, 2.4% and 8.0% higher at 24 h postsurgery, and 75.1% and 57.8% higher at 10 days postsurgery, compared with patients receiving cryoprecipitate without TEEs and patients receiving HFC, respectively. Similar results were seen for VWF antigen levels.

4 | DISCUSSION

The present subset analysis of the FORMA-05 study reflects that although there was broad overlap in coagulation factor levels between patients who received HFC versus cryoprecipitate during the postoperative period, distinctive patterns seemed to be present for patients who developed TEEs (all in the cryoprecipitate group). The two patients who developed DVT appeared to have a procoagulant status preoperatively, with distinctively higher levels of plasma fibrinogen, FIBTEM A20, and platelets, which persisted intra- and postoperatively. The five patients who developed PE appeared to have slightly higher VWF levels preoperatively, followed by a disproportionate increase intraoperatively (postpryoprecipitate administration) and postoperatively, compared with patients on cryoprecipitate without TEEs or patients on HFC.

In this analysis, DVT occurred in two patients who displayed a hypercoagulable state even before surgery, consistent with a hypercoagulable state being not uncommon in cancer patients.[22] The results from this analysis imply that patients at risk of developing DVT could potentially be identified by screening patients preoperatively for such markers of hypercoagulation, and specific additional measures of DVT prophylaxis considered early on. A study by Dranichnikov et al.[23] in patients undergoing CRS with hyperthermic intraperitoneal chemotherapy identified through multivariate analysis that D-dimer level on postoperative Day 2 was an independent risk factor for postoperative TEE, which could provide the basis for a further assessment to identify patients at risk. Without further studies, assumptions cannot be made on whether the source of fibrinogen may influence the postoperative course of DVT in surgical patients with acquired hypofibrinogenemia.

In contrast, patients who developed PE did not seem to show any specific features in their preoperative coagulation profiles. However,

they did subsequently appear to show a higher increase in VWF:RCo activity and VWF antigen levels compared with patients who did not develop PE. A number of other studies have suggested that VWF is associated with TEEs.[24–26] For example, the prospective LITE study,[26] which included 19,237 patients aged 45–64 years, who experienced a total of 159 venous thromboembolisms (VTEs), found a dose-dependent relationship between plasma VWF levels and risk of VTE. Elevated FVIII was also cited as an independent risk factor, although mean FVIII levels were not found to be increased in patients in our study. Studies in mice have shown that VWF plays a key role in venous thrombus formation, whereby VWF-mediated platelet recruitment to the vascular wall is an important step in its initiation.[27] Although the causality of the PEs in this study could be due to multiple factors, including extensive surgery and malignancy, the finding of increased levels of VWF in these patients suggests that caution when using products which might contain additional VWF, such as cryoprecipitate, may be preferable in this type of surgery.

The main limitation of this posthoc analysis was the limited sample size, which impacts the generalizability of the suspected relationship between the increase in VWF:RCo activity and VWF antigen levels and PE. For a complete evaluation of the interaction between coagulation parameters and postoperative complications, the follow-up duration after surgery could be further extended in future investigations. Due to the rarity of the disease, data collection through registries may provide a feasible option for confirming whether the VWF content of cryoprecipitate is indeed related to the development of postoperative thromboembolic complications.

4.1 | Conclusions

These analyses show broad overlaps in plasma levels of coagulation factor between treatment with HFC and cryoprecipitate, with plasma fibrinogen, FXIII, and FVIII sufficiently maintained during and following surgery in both study groups. However, possible differences were seen in the coagulation profiles of patients who experienced TEEs during the study, compared with other patients on cryoprecipitate, who did not experience TEEs or patients on HFC. These potential differences included a persistent procoagulant status in patients who experienced DVT and a disproportionate intra- and postoperative increase in VWF in patients who experienced PE. Larger studies in diverse surgical settings are needed and should record coagulation factor levels throughout and following surgery alongside reported TEEs to gain a better understanding of which patients are more at risk for TEE and which patient- or treatment-related factors may influence that risk.

AUTHOR CONTRIBUTIONS

Ashok Roy: Conceptualization; funding acquisition; investigation; methodology; resources; supervision; writing—review and editing. **Nigel Sargant**: Investigation; writing—review and editing. **John Bell**: Investigation; writing—review and editing. **Sophia Stanford**: Data curation; investigation; project administration; resources; writing—review and editing. **Cristina Solomon**: Conceptualization; supervision; writing—review and editing. **Irina Kruzhkova**: Methodology; project administration; resources; supervision; writing—review and editing. **Sigurd Knaub**: Conceptualization; methodology; writing—review and editing. **Faheez Mohamed**: Conceptualization; funding acquisition; investigation; methodology; resources; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

A.R. and F.M. have received investigator fees from Octapharma AG. N.S., S.S., and J.B., have not received support from any organisation for the submitted work. I.K., C.S., and S.K. are employees of Octapharma AG.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

ETHICS APPROVAL STATEMENT

The study was approved by the National Health Service Health Research Authority, South Central - Hampshire A Research Ethics Committee in the UK (Ref: 16/SC/0576) and was conducted in accordance with the Declaration of Helsinki.

CLINICAL TRIAL REGISTRATION

The FORMA-05 study is registered with the European Union Clinical Trials Register (EudraCT Number 2016-003749-27).

TRANSPARENCY STATEMENT

The lead author Faheez Mohamed affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ORCID

Faheez Mohamed http://orcid.org/0000-0002-0097-2075

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