

Factor VIII Inhibitor Bypass Activity (FEIBA) for the Reduction of Transfusion in Cardiac Surgery: A Randomized, Double-Blind, Placebo-Controlled, Pilot Trial

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Abstract

Background Uncontrolled bleeding after cardiac surgery can be life threatening. Factor eight inhibitor bypassing activity (FEIBA) is a prothrombin complex concentrate empirically used as rescue therapy for correction of refractory bleeding diathesis post cardiopulmonary bypass (CPB). FEIBA use as rescue therapy for bleeding diathesis after CPB has been associated with a low incidence of complications and a reduction in transfusion requirement and re-exploration. The feasibility and efficacy of early administration of FEIBA after termination of CPB have not been studied.

Methods We designed a small randomized, double-blinded, placebo-controlled pilot trial to determine the feasibility of a larger trial testing the hypothesis that FEIBA decreases transfusion requirements after CPB. Twelve adult patients undergoing elective major aortic cardiovascular surgery at a tertiary referral hospital were equally randomized to receive a single dose of either FEIBA or matched placebo intraoperatively at the end of CPB. The study was designed to evaluate the feasibility of a larger pivotal trial to determine the effectiveness of FEIBA in reducing the total volume of blood products transfused perioperatively, and its safety profile.

Results There were no protocol deviations or events of unblinding, and adverse events were not different between groups. Patients in the FEIBA group were older, more likely to be female, had higher BMI, lower hematocrit, and longer hypothermic circulatory arrest. There were no differences in post randomization blood product transfusions (difference FEIBA vs. placebo: -899 mL; 95%CI: -5,206 to 3,409, $p = 0.65$).

Conclusions This pilot trial confirmed the adequacy of the trial design that involved the early, blinded administration of FEIBA, by demonstrating excellent protocol adherence. We conclude that a larger trial establishing the effectiveness of early prothrombin complex concentrate administration to reduce the use of blood products in the setting of high-risk cardiac surgery is feasible.

Trial Registration: ClinicalTrials.gov Identifier: NCT02577614

Background

It is recognized that blood product transfusion has been associated with adverse outcomes in cardiac surgery, including increased risk of infection, hospital length of stay, and mortality. While cardiac surgeons and anesthesiologists appreciate the risk of morbidity and mortality with blood product transfusion [1–7], it is challenging to find alternative strategies to correct bleeding diathesis after cardiopulmonary bypass (CPB). Current prophylactic management of CPB-associated bleeding diathesis is by infusion of antifibrinolytic medications, such as tranexamic acid and ϵ -aminocaproic acid. However, refractory bleeding still occurs despite the use of antifibrinolytics.

In cardiac surgical procedures at high risk for bleeding after separation from CPB such as those involving the aorta with long CPB and aortic cross-clamp times, refractory bleeding diathesis is commonly managed with the initiation of rescue therapy with recombinant activated factor VII. The evidence for

prothrombin complex concentrate products, albeit limited, suggests decreased intraoperative transfusion requirements [8, 9]. However, there are also substantial risks which include stroke or other thrombotic events which may be life threatening [10].

Factor eight inhibitor bypassing activity (FEIBA) is principally composed of the clotting factors of the prothrombin complex, chiefly Factors II, VII, IX and X. Whereas in licensed Prothrombin Complex Concentrates (PCC) the coagulation factors are present as zymogens, FEIBA does contain small amounts of activated coagulation factors, in addition to the zymogens [11, 12]. Furthermore, PCC's contain Protein C and S as a safeguard against undesired coagulation activation, plus added heparin/antithrombin complex. PCC's are essentially used to replace a deficit in clotting factors, whereas FEIBA is designed to directly trigger the clotting process. The mechanism of action is linked to the prothrombinase complex, and to the interaction between prothrombin (F II) and activated factor X (F Xa). Feiba is currently approved for use in the United States for the treatment of patients with hemophilia and inhibitors at a dose of 50–100 IU/kg. There is some evidence demonstrating the safety and efficacy of FEIBA for hemophilia patients with inhibitors [11, 13], as well as for the reversal of warfarin, dabigatran, rivaroxaban, and other anticoagulation products [12, 14, 15]. FEIBA has a theoretical advantage compared to activated factor VII in that it replenishes multiple depleted factors that are lost with CPB. This factor replenishment with FEIBA may lead to improved hemostasis, possibly with lower thrombotic risk compared to activated factor VII [4–8, 10, 13–20].

Our institution has experience with the use of FEIBA for the rescue treatment of CPB associated coagulopathy. We recently reported that FEIBA, used as rescue therapy for post CPB bleeding diathesis with a conservative dose of 10–25 IU/kg (average of 2,100 IU total dose per patient), was associated with a low incidence of complications and sharply reduced transfusion requirement as well as the need for re-exploration due to ongoing hemorrhage [18].

We conducted a pilot study to evaluate the feasibility of the prophylactic administration of FEIBA after termination of CPB and a reversal dose of IV protamine sulfate. The study was designed to demonstrate the potential role of FEIBA administration in reducing the need for allogeneic transfusion to treat refractory bleeding diathesis in patients undergoing high risk cardiovascular surgery.

Methods

Study Design

We conducted a single center, double blind, placebo controlled, randomized pilot trial to assess the feasibility and safety of prophylactic FEIBA administration in patients undergoing elective major aortic cardiovascular surgery requiring CPB. The study was conducted at Oregon Health and Science University adult cardiac operating rooms between August 1, 2016 and August 31, 2017. The study protocol was approved by the Institutional Review Board. Patients were enrolled in the trial after providing written informed consent preoperatively. The study adheres to CONSORT guidelines.

Study Population

Patients were eligible if they were adults 18 years or older, scheduled for elective aortic procedures, including ascending, arch, and descending repair or reconstruction, with cardiopulmonary bypass, aortic valve repair or replacement, coronary re-implantation (Bentall) and/or deep hypothermic circulatory arrest. Patients were excluded if they were unable to receive the study drug based on contraindications stated by the manufacturer, such as known anaphylactic or severe hypersensitivity reactions to FEIBA or any of its components or received a blood transfusion within 28 days. Patients were also excluded if their scheduled procedure included coronary artery bypass grafting, had history of myocardial infarction, thrombosis or embolism, disseminated intravascular coagulation, or were pregnant women, decisionally impaired, prisoners, or unwilling to provide informed consent.

Randomization and blinding

A random list equally assigning patient to either FEIBA or placebo was generated using a uniform distribution, maintained and assigned by the investigational pharmacy. Patients, surgeons, anesthesiologists, and nurses were blinded to treatment assignment. The research pharmacy prepared the FEIBA (at the concentration of 40 IU/mL) or placebo (normal saline) in an opaque syringe. To maintain blinding, the volume of FEIBA and the matched placebo were prepared based on an mL per kg basis. Blinded assessors collected data on primary and secondary endpoints, including transfusion requirements, safety endpoints, and protocol adherence auditing.

Study groups

After anesthesia induction, patients were equally randomized to receive either a single dose of FEIBA or a matched volume of saline administered after separation from CPB. The active study drug was prepared in the dose of 20 IU per kilograms in a concentration of 40 IU/mL, at a rate of 0.5 mL/kg via infusion pump over 10 minutes. The placebo consisted of a matched volume of 0.9% sodium chloride supplied in an identical syringe and tubing at a rate of 0.5 mL/kg via infusion pump over 10 minutes. Patients were otherwise managed per usual care according to a standardized protocol.

Study procedures

After separation from CPB, a reversal dose of intravenous protamine sulfate, calculated according to the heparin dose response curve, was given with a target goal of a heparin concentration of zero or a return to baseline activated clotting time (ACT). As part of our standard care, routine post CPB labs, a complete blood count and coagulopathy panel including hemoglobin, hematocrit, platelet count, INR, aPTT and fibrinogen were sent after the administration of IV protamine immediately following separation from CPB, with a post protamine ACT and arterial blood gas. In addition, samples were collected for thromboelastogram (TEG) by the research lab. After ACT normalized and labs were drawn, the study drug was administered, and the field was subsequently inspected for ongoing microvascular bleeding. In the presence of refractory bleeding diathesis, the anesthesiologist was permitted to administer a dose of

FEIBA in an open label manner as a rescue measure based on the algorithm described below and illustrated in Fig. 1. Patients who experienced hemorrhage received, as first line, standard therapy with blood products including fresh frozen plasma (FFP), platelets and packed red blood cells (PRBCs). Up to 1 apheresis platelets and 2 FFPs could be administered empirically, then additional products were administered based on coagulation panel (target INR \leq 1.7 and aPTT \leq 50 sec). PRBCs were administered with the goal of maintaining a hemoglobin level \geq 7 mg/dL. If refractory bleeding persisted after the empiric or laboratory-based administration of at least 4 units of FFPs and 2 apheresis platelets, then rescue therapy of 10–20 IU/kg (or 1,500 units for patients > 150 kg) of open-label FEIBA was given to patients who displayed refractory bleeding diathesis. Subsequently, after the administration of FEIBA, cryoprecipitate and lab guided administration were continued. The study was designed such that the total dose of FEIBA would not exceed 40 IU/kg (including the presumed 20 IU/kg given as study drug). The supply of FEIBA for open label use was prepared by the anesthesiologist according to manufacturer recommendations.

Sample size

We planned to enroll 12 patients for the initial feasibility and safety study. As this study was designed to evaluate the feasibility and safety of FEIBA administration in the setting of high-risk cardiovascular surgery with CBP, it did not have adequate power for efficacy endpoints.

Study endpoints

The primary goal of this pilot trial was to document the feasibility of the prophylactic blinded administration of FEIBA in the context of cardiovascular procedures at high risk of coagulopathy and requirement for blood product transfusion. Indicators of feasibility were protocol violations, maintenance of blinding, use of open label FEIBA, and occurrence of serious adverse events. The primary endpoints for a larger pivotal trial would be cumulative volume of blood products transfused including packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and use of cryoprecipitate, after the administration of the study drug until the end of anesthesia, and the evaluation of the safety profile.

Statistical Analysis

The study was analyzed using a modified intention-to-treat approach. Descriptive summaries are presented using means and standard deviations (SD) for quantitative characteristics and frequencies (%) for categorical characteristics. Since the study design was randomized, we tested for treatment differences using Welch's t-tests for mean comparisons of quantitative characteristics and chi-square tests of associations for binary or categorical characteristics. Welch's t-test was used to test for a treatment effect for the primary endpoint, volume in mL/kg body weight of any blood products transfused after randomization, and for the secondary endpoints. There were no plans for interim analysis, however, safety data was monitored on an ongoing basis during the study. All hypothesis tests evaluated were two-sided, and all analyses were conducted using the Stata (version 15.1) statistical

package. The same statistical package was used to create the random sequence for the fair-coin randomization assignment.

Results

Demographic and baseline characteristics

Twenty patients were screened for eligibility and 13 patients were randomized. Six were allocated to the placebo group and 7 were allocated to the FEIBA group (Fig. 2). One subject in the FEIBA group was randomized in error, did not receive study drug, and was excluded. Subject baseline characteristics are shown in Table 1, demonstrating unbalances between the FEIBA and the placebo groups in some patients' demographics, including mean age (63 years versus 49 years) and mean BMI (33 versus 26). Furthermore, the FEIBA group had more females (67% versus 0%) and more patients with hypertension (100% versus 50%) compared to the placebo group. The hematocrit was lower in the FEIBA group compared to the placebo group (39% vs 43%). All other baseline characteristics were similar between groups.

Table 1

Patients' baseline characteristics stratified by treatment assignment. Data are expressed as mean (SD), unless otherwise specified.

	FEIBA n = 6	Placebo n = 6
Age, years	62.5 (4.3)	49.2 (13.1)
Gender, n (% female)	4 (67)	0 (0)
Weight, kg	101 (20.0)	84 (9.5)
Height, cm	175 (7.6)	180 (8.4)
Body mass index, kg/cm ²	33 (5.0)	26 (4.4)
Non-Hispanic, n (%)	6 (100)	5 (83)
Diabetes, n (%)	0 (0)	1 (17)
Hypertension, n (%)	6 (100)	3 (50)
Smoking status, n (%)	3 (50)	2 (33)
CVA, n (%)	2 (33)	0 (0)
Anti-platelet therapy, n (%)	4 (67)	2 (33)
ASA score \geq 4, n (%)	6 (100)	4 (67)
Baseline labs		
BUN	20 (9.4)	19 (2.8)
Creatinine (mg/dL)	0.89 (0.3)	1.13 (0.2)
Hematocrit (%)	39 (1.7)	43 (2.5)
Platelet count (K/cu)	203 (62)	194 (16)
APTT	44 (34)	27 (3)
INR	1.05 (0.1)	1.01 (0)
Fibrinogen (mg/dL)	403 (63)	337 (100)
FEIBA, Factor eight inhibitor bypass activity; CVA, Cerebrovascular accident; ASA, American Society of Anesthesiology physical status; BUN, Blood urea nitrogen; APTT, Activated partial thromboplastin time; INR, International normalized ratio.		

Intraoperative characteristics are shown in Table 2. The mean duration of deep hypothermic cardiac arrest (93 min versus 24 min) was longer in the FEIBA group compared to the placebo group. All other intraoperative characteristics were similar between groups.

Table 2
Intraoperative characteristics stratified by treatment assignment, mean (SD).

	FEIBA n = 6	Placebo n = 6	P-value
Cardiopulmonary bypass duration, min	276 (111)	170 (53)	0.06
Aortic cross clamp time, min	159 (75)	123 (51)	0.35
Lowest temperature during CPB, °C	25 (4)	25 (4)	0.86
Deep hypothermic cardiac arrest, n (%)	5 (83)	3 (50)	0.22
Deep hypothermic cardiac arrest duration, min	93 (26)	24 (5)	< 0.01
FEIBA study drug dose, IU, mean (SD)	1,902 (499)	0	< 0.01
Open label FEIBA, n (%)	2 (33)	1 (17)	0.51
Dose, IU, mean (SD; n1 = 2; n2 = 1)	3,772 (1,002)	1,840 (-)	-
Dose, IU, mean (SD; n1 = 6; n2 = 6)	1,241 (2,024)	307 (751)	0.31
FEIBA, Factor eight inhibitor bypass activity; CPB, cardiopulmonary bypass.			

Study endpoints: During the study implementation, protocol adherence was high, without protocol violations, with the exception of one patient randomized in error. The administration of open label FEIBA was not different between the two groups. Additional study endpoints to estimate variability for the planning of a larger trial are shown in Table 3. There was substantial variability but no difference in the endpoint of total volume of blood product transfused post-randomization (difference between FEIBA and placebo group - 899 mL (95% CI: -5,205.7 to 3,408.7)). Likewise, there were no difference in the individual blood components or in the amount of post-randomization blood product transfused intraoperatively or in the ICU. There were no differences in TEG values before and after study drug administration and between the two groups (Table 4). The volume of chest tube drainage, duration of intubation and hospital length of stay were not different between FEIBA and placebo group (Table 3).

Table 3

Study primary and secondary endpoints. Data are expressed as mean (SD), unless otherwise specified.

Variable	FEIBA n = 6	Placebo n = 6	Difference (95% Confidence Interval)	P- value
Volume of all blood products transfused, mL	3,126 (3,710)	2,227 (3,710)	-899 (-5,205.7 to 3,408.7)	0.65
Blood product transfused intraoperatively				
Packed red blood cells, n (%)	4 (67)	0 (0)		0.01
Packed red blood cells, mL	572 (552)	0 (0)	-572 (-1,073.7 to -69.6)	0.03
Fresh frozen plasma, n (%)	4 (67)	4 (67)		> 0.99
Fresh frozen plasma, mL	981 (857)	338 (288)	-643 (-1,465.2 to 179.2)	0.11
Platelets, n (%)	6 (100)	5 (83)		0.30
Platelets, mL	952 (511)	437 (308)	-515 (-1,057.2 to 27.2)	0.06
Cryoprecipitate, n (%)	3 (50)	0 (0)		0.05
Cryoprecipitate, mL	171 (210)	0	-171 (-362.2 to 20.2)	0.07
Blood product transfused in the ICU				
Packed red blood cells, n (%)	1 (17)	1 (17)		> 0.99
Packed red blood cells, mL	175 (429)	572 (1,400)	397 (-935.4 to 1,728.8)	0.52
Fresh frozen plasma, n (%)	1 (17)	1 (17)		> 0.99
Fresh frozen plasma, mL	102 (250)	437 (1070)	335 (-664.7 to 1,333.7)	0.47
Platelets, n (%)	1 (17)	1 (17)		> 0.99
Platelets, mL	49 (119)	83 (204)	35 (-179.8 to 249.2)	0.73
Cryoprecipitate, n (%)	1 (17)	1 (17)		> 0.99
Cryoprecipitate, mL	21 (51)	79 (194)	58 (-123.9 to 240.2)	0.40
Patients requiring re-exploration, n (%)	1 (17)	1 (17)		> 0.99

FEIBA, Factor eight inhibitor bypass activity; ICU: Intensive Care Unit

Variable	FEIBA n = 6	Placebo n = 6	Difference (95% Confidence Interval)	P- value
Chest tube drainage at 8 hours, mL	282 (110)	611 (860)	329 (-459.3 to 1,117.3)	0.37
Chest tube drainage at 24 hours, mL	725 (559)	913 (1028)	188 (-876.1 to 1,252.4)	0.70
ICU intubation, hours	87.2 (162.6)	8.2 (6.2)	-79 (-249.6 to 91.6)	0.29
Length of ICU stay, hours	333.5 (670.7)	74.3 (51.1)	259.2 (-962.7 to 444.4)	0.39
Length of hospital stay, days	20.3 (25.7)	5.7 (1.0)	14.7 (-41.6 to 12.3)	0.22
FEIBA, Factor eight inhibitor bypass activity; ICU: Intensive Care Unit				

Table 4

Pre- and post- study drug hematological and coagulation profile. Data are expressed as mean (SD), unless otherwise specified.

	Prior to Study Drug			Post Study Drug		
	FEIBA n = 6	Placebo n = 6	P- value	FEIBA n = 6	Placebo n = 6	P-value
R value, min	7.78 (1.83)	6.63 (1.75)	0.32	5.5 (1.29)	5.17 (1.27)	0.68
K, min	2.34 (1.99)	2.35 (0.69)	0.99	2.58 (1.88)	2.12 (1.21)	0.63
α angle, degrees	66 (15)	61 (7)	0.49	65 (12)	63 (12)	0.84
MA, mm	53 (13)	55 (6)	0.69	55 (12)	60 (6)	0.42
A, mm	53 (12)	55 (5.2)	0.62	55 (13)	59 (5)	0.56
CI	-2.3 (3.9)	-1.6 (2.3)	0.72	0.32 (3.0)	0.17 (2.8)	0.91
LY 30	0.2 (0.3)	0.03 (0.1)	0.19	0.04 (0.05)	0.13 (0.33)	0.55
Hematocrit	27.3 (25.0)	27.7 (24.4)	0.81	28.6 (22.8)	29.7 (22.4)	0.75
Platelets	98 (60)	114 (25)	0.56	135 (67)	168 (40)	0.31
INR	2.2 (0.7)	1.8 (0.2)	0.17	1.38 (0.3)	1.50 (0.1)	0.38
APTT	48 (23)	36 (10)	0.25	45 (15)	35 (5)	0.13
Fibrinogen	189 (117)	189 (53)	>0.99	220 (104)	194 (43)	0.62
FEIBA, Factor eight inhibitor bypass activity; R, reaction time; K, coagulation time; MA, maximum amplitude; A, amplitude; CI, Coagulation index; LY 30, amplitude at 30 min; INR, International normalized ratio; APTT, Activated partial thromboplastin time						

There were a total of five serious adverse events in two patients resulting in death. One patient experienced postoperative complications including acute kidney failure requiring renal replacement therapy, and cerebrovascular accident. The other patient had refractory bleeding diathesis and bleeding after separation from CPB requiring the administration of open label FEIBA. Postoperatively, the patient developed a cerebrovascular accident (Table 5). These events were considered not related to the study drug.

Table 5
Safety and adverse events, number of events (%).

	FEIBA n = 6	Placebo n = 6	P-value
Number of patients with AEs	2	0	
30-day mortality	2 (33)	0	0.12
Cerebrovascular accident	2 (33)	0	0.12
Thromboembolism	0	0	na
Deep vein thrombosis / pulmonary embolism	0	0	na
Myocardial infarction	0	0	na
Renal replacement therapy	1 (17)	0	0.30
FEIBA, Factor eight inhibitor bypass activity; AEs, Adverse Events			

Discussion

In this small pilot trial evaluating the feasibility of prophylactic administration of FEIBA in a blinded fashion, we found that it was possible to comply with study procedures and adhere to the study protocol, with patients assigned to the FEIBA group receiving the active study drug in the appropriate dose, while open label use of rescue FEIBA was limited to refractory bleeding diathesis, according to the study algorithm.

Due to the small sample size, the randomization did not produce equally balanced groups, with the FEIBA group resulting in an older population with more comorbidities and longer duration of deep hypothermic circulatory arrest. Although not different between the two groups, not surprisingly more serious adverse events were reported in the FEIBA group.

The study was not powered to detect differences in the efficacy endpoint of total amount of blood product transfused after randomization. However, the study provides estimates of variability that will allow the calculation of the sample size for the pivotal efficacy study.

We failed to find differences in the cumulative amount of blood product transfused or in the amount transfused intraoperatively or in the ICU. This is in contrast with prior findings from observational studies suggesting relevant reduction in blood component transfusion [18]. Several considerations might explain this finding, including the high variability in the volume of blood product transfused across the study population overall, the small sample size, and the relative low percentage of patients requiring transfusion despite the complex surgical procedures considered at high risk of bleeding diathesis after completion of CPB.

This trial provides important insights to inform the planning of the pivotal trial including the population selection to include patients who are more likely to require transfusion and the determination of the appropriate dose of FEIBA. Because we did not detect differences in coagulation profile between the groups after the administration of the study drug, the dose of FEIBA administered for the study may have not been adequate. It is possible that a higher dose might have resulted in more detectable changes in the coagulation profile. It is also possible that correction of the coagulation profile in the placebo group occurred by replenishing factor deficiency derived from other sources such as blood components. Due to the unbalances in baseline and intraoperative characteristics, it is challenging to further interpret differences between groups with regard to blood product transfused. It should be emphasized that bleeding complications typically have a multifactorial origin. To what extent FEIBA treatment may reduce bleeding and transfusion requirements would require a larger clinical trial.

While this trial was not powered to detect differences between groups, future trials will need to be powered to assess comparative outcomes including cumulative volume of blood products transfused. If alternatives to packed red blood cells, fresh frozen plasma, and platelet transfusion were available, complications could potentially be reduced. Prothrombin complex concentrates may turn out to be a lower-risk alternative to the blood products from which they are derived.

Conclusions

We demonstrated the feasibility of a double-blind, placebo-controlled trial to test whether administration of prophylactic FEIBA decreases transfusion of blood products in patients at high risk for bleeding diathesis in cardiac surgery. Although the trial was not powered for the evaluation of efficacy, the study provides estimates of variability for the planning of a pivotal trial. We conclude that a larger trial of prophylactic FEIBA administration to prophylactically replenish coagulation factors and correct post CPB coagulopathy is feasible; however, further refinements of the study design are needed specifically with regard to the study population selection and the choice of study drug dosing. Whether a prophylactic approach might prevent refractory bleeding diathesis and reduce the need for high volumes of blood product transfusion needs to be determined in a future, larger trial. Due to the morbidity associated with blood product transfusion [21], and their limited supply availability, identifying alternate strategies to manage post-CPB bleeding diathesis is an important and valuable goal.

List Of Abbreviations

ACT Activated clotting time

aPTT Activated partial thromboplastin time

CPB Cardiopulmonary bypass

FEIBA Factor eight inhibitor-bypass activity

FFP Fresh frozen plasma

INR International Normalized Ratio

PCCs Prothrombin complex concentrate

PLTs Platelets

PRBCs Packed red blood cells

SAE Serious adverse event

TEG Thromboelastogram

Declarations

Ethics approval and consent to participate:

The study protocol was approved by the Institutional Review Board. Patients were enrolled in the trial after providing written informed consent preoperatively.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

None

Funding:

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Authors' contributions:

Study design: VAS, AES, MMT

Acknowledgements:

Not applicable

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Figures

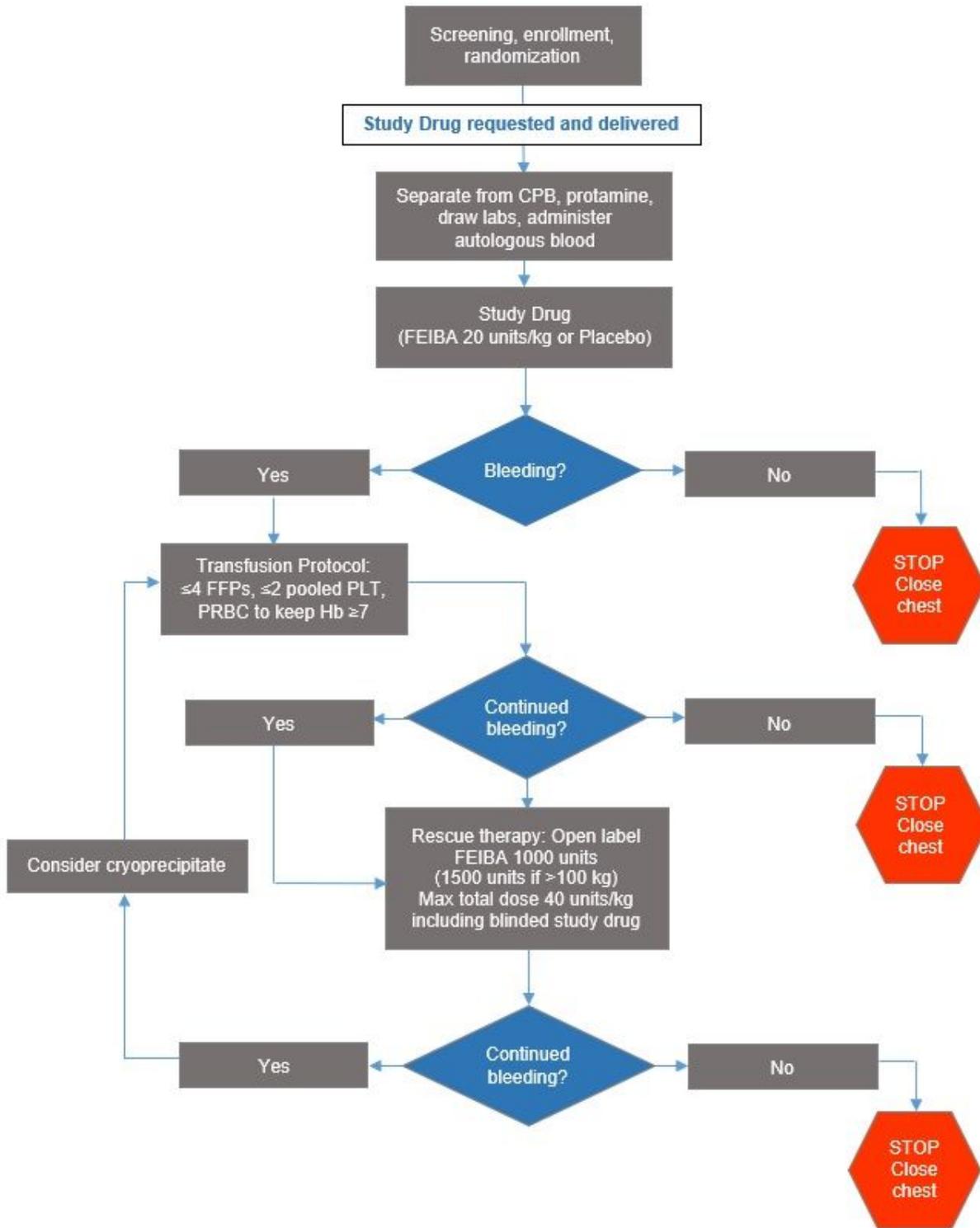


Figure 1

Study design and decision algorithm to guide the management of bleeding diathesis after separation from cardiopulmonary bypass (CPB). FEIBA: Factor VIII Inhibitor Bypass Activity; FFPs: Fresh Frozen Plasma; PLT: Platelets; PRBCs: Packed Red Blood Cells.

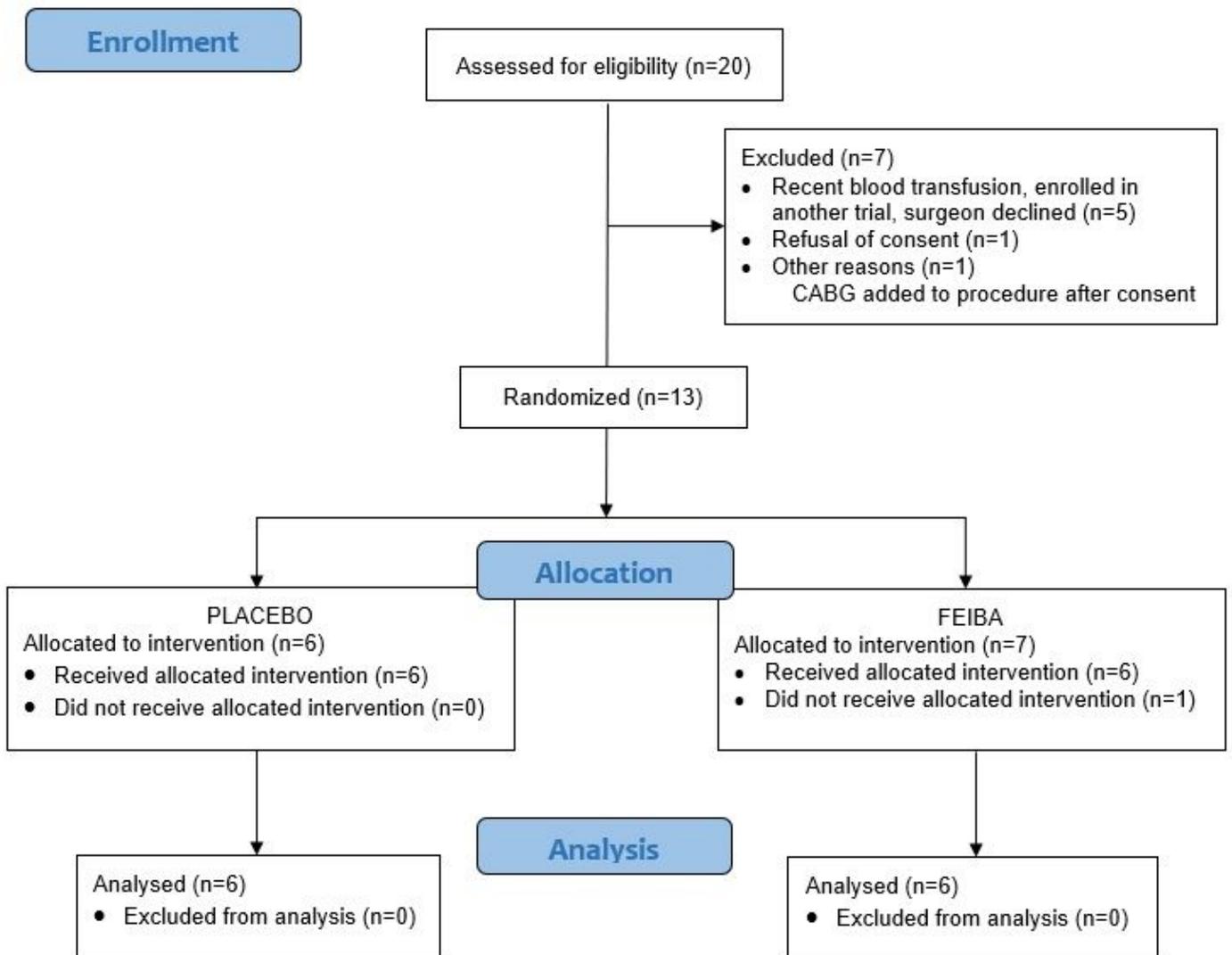


Figure 2

Study flowchart.

Supplementary Files

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- [CONSORT2010ChecklistMSWord.doc](#)