Perioperative Use of Activated Prothrombin Complex Concentrates

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Surgical bleeding poses a risk during both routine and complex procedures. Patients can experience bleeding related to the nature or invasiveness of the procedure itself, but also due to preexisting conditions such as congenital/acquired bleeding disorders, the use of anticoagulants, or acquired coagulopathy from trauma-induced blood vessel damage, organ dysfunction, or hemodilution. Major perioperative bleeding is generally managed with diligent local hemostatic measures, the transfusion of blood products to replete coagulation factors and platelets, and the use of pharmacologic adjuncts such as antifibrinolytic medication (*e.g.*, tranexamic acid) to promote the formation of a stable hemostatic clot. Coagulation factor concentrates are increasingly being used in an off-label fashion to promote and accelerate effective hemostasis in the setting of severe bleeding. Prothrombin complex concentrates (PCCs), activated PCCs (aPCCs), and recombinant activated factor VII (rFVIIa) have all been used to treat refractory perioperative bleeding. However, the balance between efficacy in controlling bleeding and the risk of thrombosis is a critical consideration in the clinical use of factor concentrates, particularly those containing activated factors (*i.e.*, rFVIIa and aPCCs). Although aPCC is increasingly being used to optimize perioperative hemostasis and to treat surgical bleeding, there are limited data currently to directly support its use in this setting. Herein, we review aPCC's composition, its proposed mechanisms of action, and historical and recent uses, as well as emerging data on its limited application in treating perioperative coagulopathy and cardiac surgical bleeding. OpenAI's (USA) ChatGPT 4o was used to describe the methodology and generate a summary of individual, published journal articles cited in the text.

History and Background of aPCC

PCCs were first used to treat patients with factor IX (FIX) deficiency (hemophilia B).[1] The clinical efficacy of PCCs in patients with hemophilia and inhibitors was attributed to small amounts of coagulation factors present in activated form in traditional nonactivated PCCs.[1,2] This led to the development of formal aPCCs ("auto-IX complex") by subjecting PCCs to various activation conditions (exposure to tissue factor, factor V, calcium, Russel's viper venom, or silica).[3] The only U.S. Food and Drug Administration (FDA; Silver Spring, Maryland)–approved aPCC formulation in the United States is factor eight inhibitor bypassing activity (FEIBA, Takeda Pharmaceuticals U.S.A., Inc., USA). FEIBA was originally developed as a therapeutic product to be used in the management of patients with hemophilia A or B who have formed inhibitory antibodies against factors VIII (FVIII) or IX (FIX), and carries FDA approval specifically for this indication.[4] This review will explore the safety and efficacy data on the off-label use of aPCCs, with a particular focus on their use as adjuncts to treat refractory perioperative bleeding.

aPCCs are complex, plasma-derived, multicomponent products containing a mixture of activated and nonactivated clotting factors used to promote hemostasis in patients with bleeding disorders.[1] Available for clinical use since 1976, FEIBA contains vitamin K–dependent coagulation factors separated from pooled, cryoprecipitate-poor, plasma. The factors are then concentrated by nanofiltration and subjected to a two-step vapor heat-treatment procedure for inactivation of lipid- and non–lipid-enveloped viruses.[4] FEIBA is produced by subjecting PCC to a proprietary "activation step" to generate a significant fraction of activated factor VII (FVIIa), in addition to smaller fractions of

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Abbreviations: aPCC, activated prothrombin complex concentrate; **CPB**, cardiopulmonary bypass; **DOAC**, direct oral anticoagulant; **DVT**, deep vein thrombosis; **FDA**, U.S. Food and Drug Administration; **FEIBA**, factor eight inhibitor bypassing activity; **FIX**, factor IX; **FIXa**, activated factor IX; **FVIIa**, activated factor VII; **FVIIIa**, activated factor VIII; **FXa**, activated factor X; **FVII**, factor VII; **FVIII**, factor VIII; **ICH**, intracerebral hemorrhage; **INR**, international normalized ratio; **PCC**, prothrombin complex concentrate; **rFVIIa**, recombinant activated factor VII; **ROTEM**, rotational thromboelastometry; **TGA**, thrombin generation assay; **VKA**, vitamin K antagonist

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Table 1. aPCC Hemostatic Components

Component	Units per 1 U FEIBA
Prothrombin (factor II)	1.3 ± 0.3
Thrombin (factor IIa)	0.01 ± 0.004
Factor VII	0.9 ± 0.1
Factor VIIa	1.5 ± 0.2
Factor IX	1.4 ± 0.1
Factor IXa	approximately 0.0006
Factor X	1.1 ± 0.2
Factor Xa	0.06 ± 0.002
Factor VIII	0.03–0.1
Factor V	approximately 0.6
Protein C	1.1 ± 0.2
Protein S	approximately 0.4
TFPI	10–3 (ng)

One unit factor eight inhibitor bypassing activity (FEIBA) is defined as the amount of FEIBA capable of shortening the activated partial thromboplastin time of high-titer factor VIII inhibitor plasma by 50%. Adapted from Brackmann *et al.*[1]

aPCC, activated prothrombin complex concentrate; TFPI, tissue factor pathway inhibitor.

activated factors X (FXa), IX (FIXa), and II (thrombin).[3,5] Additionally, FEIBA contains the inactive zymogens of coagulation factors II (prothrombin), factor VII (FVII), FIX, factor X, and the anticoagulant protein C, in addition to small amounts of factor V, factor VIII (FVIII), protein S, and tissue factor pathway inhibitor (table 1).[1,6] One unit (U) of FEIBA is defined as the amount of concentrate that shortens the activated partial thromboplastin time of a reference plasma sample containing high-titer FVIII inhibitor by 50%.

Mechanism of Action

FEIBA addresses challenges in hemophilia patients who have developed inhibitory antibodies to FVIII (hemophilia A) or FIX (hemophilia B). These antibodies bind to epitopes of infused clotting factors, effectively neutralizing their procoagulant activity, rendering standard replacement therapy ineffective. FEIBA's mechanism in this setting has been described as a "bypassing activity," which describes its ability to enable coagulation to proceed through pathways independent of the propagation phase. The propagation phase of coagulation relies heavily on the tenase complex, comprised of both factor VIIIa (FVIIIa) and FIXa, and whose activity is impaired in both hemophilia A and hemophilia B. By bypassing the need for FVIIIa or FIXa, FEIBA allows for the formation of a hemostatic thrombotic plug in the presence of FVIII or FIX inhibitors. This mechanism is particularly beneficial during bleeding episodes, where rapid and effective clot formation is essential to prevent excessive blood loss.

Most attempts at elucidating FEIBA's mechanism of action have been in the context of FVIII or FIX inhibitors in patients with hemophilia. Many of these mechanisms are likely also important for producing FEIBA's general prohemostatic effect in patients treated off-label for life-threatening surgical bleeding. The precise hemostatic mechanisms by which FEIBA generates bypassing activity are unclear,[7,8] although several mechanisms have been proposed over the course of four decades of clinical use for hemophilia (fig. 1). Conventional pharmacokinetic methods (absorption, distribution, metabolism, elimination) cannot adequately characterize FEIBA's effects because of its multicomponent and complex nature. Thrombin generation assays (TGAs; fig. 1) continuously measure the production of thrombin through the cleavage of a fluorogenic substrate.[9] They provide information on both kinetic and quantitative parameters of thrombin generation.[10,11] Kinetic parameters include the lag time (time for thrombin generation to first occur, in minutes) and the time to peak (start to maximum thrombin generation, in minutes), whereas quantitative measures include the peak height ("peak"; maximum thrombin generation, in nanomolar; nM) and the endogenous thrombin potential (area under the thrombin generation curve, in nanomolar·min; nM·min). Thrombin generation velocity is usually determined by dividing peak thrombin generation by the time difference between the time to peak and the lag time. TGAs have been instrumental in providing a better understanding of FEIBA's mechanisms of action (fig. 1).[6,12]

FEIBA's bypassing activity and prohemostatic effects had previously been attributed to the generation of procoagulant phospholipids during product activation, and it was thought that these coagulant active phospholipids might protect activated coagulation factors from inhibitors.[13,14] More recently, FEIBA's effects have been attributed to the ability of prothrombin, FXa, and FVIIa to initiate thrombin generation in the presence of inhibitors.[4] It has been established that supraphysiologic concentrations of FVIIa are able to trigger thrombin generation on the surface of activated platelets, although such levels are not achieved with standard FEIBA dosing.[5,15,16] It has also been proposed that prothrombin might protect the small quantities of FXa found in FEIBA from inhibitors.[5,17] Protection of the trace amounts of FXa required to initiate thrombin generation on the platelet surface by prothrombin might contribute to FEIBA's effects. Moreover, it has been found that high levels of prothrombin can contribute to the assembly of the prothrombinase complex (factors Xa plus Va) on phospholipid surfaces.[18] FIX may also play a role in its mode of action. It has been found that FIX zymogen might potentiate the activation of factor X in the presence of trace amounts of FIXa, even in the absence of its cofactor, FVIIIa.[19] Both FXa and FIXa can activate FVII on phospholipid micelles, independently of FVIIIa.[20] Last, FEIBA might exert its procoagulant effects simply by increasing the availability of zymogens. By increasing the availability of enzymatic substrates, more active enzyme will ultimately be generated.[5] Although each of these proposed mechanisms might be important, it is more likely that FEIBA functions through a

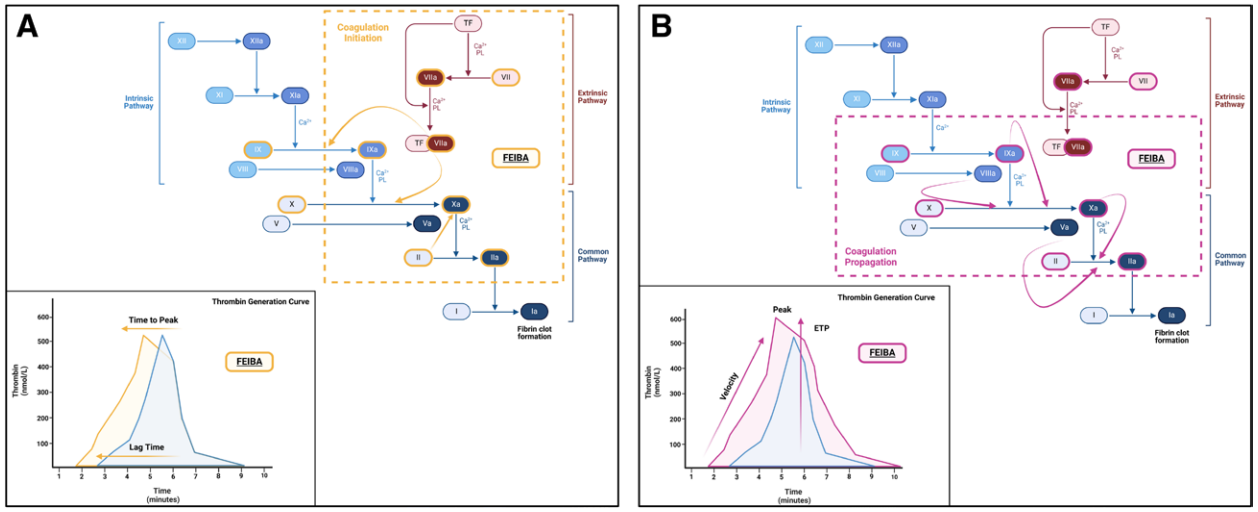

Fig. 1. Conceptual framework for factor eight inhibitor bypassing activity (FEIBA) multimodal effects on coagulation initiation and propagation. (*A*) Coagulation initiation: Tissue factor (TF) is released from injured endothelial cells and monocytes. TF and activated factor VII (FVIIa) form the TF + FVIIa complex. TF + FVIIa activate a small amount of factor IX (FIX) and factor X (FX), which generates trace amounts of thrombin (activated factor II [FIIa]). Coagulation initiation is best captured by the lag time to the first traces of thrombin generation. FEIBA might accelerate thrombin generation and shorten the thrombin generation lag time by increasing the concentrations of FVIIa, FXa, and factor II (FII). Excess FII might protect trace amounts of activated factor X (FXa) needed to initiate thrombin generation on the platelet surface. These initial steps might account for FEIBA's bypassing activity in hemophilia patients with inhibitors and enable thrombin generation to proceed despite impaired coagulation propagation. (*B*) Coagulation propagation: Activated factor IX (FIXa) complexes with activated factor VIII (FVIIIa) to form the tenase complex. The tenase complex converts large amounts of FX to FXa. FXa complexes with activated factor V (FVa) to form the prothrombinase complex, which generates large amounts of thrombin (FIIa). FEIBA increases the availability of enzymatic zymogen substrate vital to the propagation of coagulation (FIX, FVIII, FX, and FII), generating corresponding increases in peak thrombin generation, endogenous thrombin potential (ETP), and the velocity of thrombin generation.

multimodal mechanism involving, to some extent, all of the above pathways.[7]

Clinical Applications of FEIBA in Surgical Patients

Patients with Hemophilia and Inhibitors

In addition to its use to control bleeding episodes in patients with hemophilia A or B and inhibitors, FEIBA also carries an FDA indication for use in the perioperative management of such patients.[21] A prospective noninterventional multicenter study assessed 24 hemophilia patients with inhibitors undergoing 35 surgeries across various risk categories (mild, moderate, severe) at 19 centers worldwide (table 2). Hemostatic efficacy was rated as "excellent" or "good" in 91.2% of surgeries.[22] The study also documented 12 adverse events, 3 of which were serious. One adverse event (arteriovenous fistula thrombosis) was possibly related to FEIBA, while the others were deemed unrelated or mild. This study demonstrated that hemostatic control using FEIBA appears to be effective and safe for surgical interventions in patients with hemophilia and inhibitors, with a seemingly low risk of thromboembolic complications. There was variability in the FEIBA dosing and regimen, however, indicating the need for individualized treatment strategies based on patient risk and procedural bleeding risk. Similarly, a retrospective review of 37 patients receiving 112 courses of FEIBA treatment for management of acute bleeding (n = 90) or surgical hemostasis (n = 22) revealed that FEIBA was effective in 92% of cases of acute bleeding and 86% in surgical cases.[29] Median FEIBA dosing for cases involving surgical hemostasis was 100 U/kg (range, 25 to 150 U/kg), with a median administration interval of 12 h (range, 3 to 24 h). The duration of treatment for surgery ranged from 1 to 35 days, with a median of six infusions and a median cumulative dose of 450 U/kg. No adverse events or thromboembolic complications were reported. The FEIBA package insert recommends doses of 50 to 100 U/kg for perioperative management with frequency and duration of treatment to be adjusted for the type of surgical intervention. In this setting, recommendations generally state that single doses should not exceed 100 U/kg, and the maximum daily cumulative dose should not exceed 200 U/kg.[30,31]

Anticoagulant-related Bleeding

Vitamin K Antagonists

Given the success in treating bleeding in hemophilia patients, there is increasing off-label use of FEIBA to control bleeding refractory to blood product transfusion. One such population

Table 2. Summary Table – FEIBA Administration for Perioperative Optimization of Hemostasis and Major Bleeding

Study Information	Patient Population	Design	FEIBA Indication (N = Sample Size)	FEIBA Dosing	Follow-up	Clinical Hemostasis Definition	Key Results
Negrier *et al.* (2013) SURF Study[22]	Hemophilia with inhibitors	Prospective, multicenter, open-label, observational study	Perioperative hemostatic control (N = 35)	50–100 U/kg every 6 to 12 h perioperatively (maximum = 100 U/kg per dose and 200 U/kg= per day)	To hospital discharge (range = 1–29 days)	Study-specific (excellent/good /fair/poor)	Hemostatic efficacy = 91.2% (excellent/good) Thromboembolism = 2.9% (1/35; AV fistula thrombosis) Death = N/A
Pupovac *et al.* (2022)[23]	Cardiac surgery	Retrospective, single-center, propensity score–matched analysis	Perioperative hemostatic control (FEIBA N = 63/no FEIBA N = 315)	500 U with a repeat dose 500 U for continued uncontrollable bleeding (mean = 9.7 U/kg)	To hospital discharge (FEIBA mean = 12 days)	Not defined/ measured	Reoperation for bleeding (*P* Value = 0.07) FEIBA = 6.3% No FEIBA = 1.9% Thromboembolism (*P* Value = 0.36) FEIBA = 0% No FEIBA = 2.5% Mortality = 1.5% (1 of 63)
Nicholas *et al.* (2024)[24]	Cardiac surgery	Retrospective, single center, propensity score matched analysis	Perioperative hemostatic control (FEIBA N = 352/ No FEIBA N = 352)	Dosed at 250 U increments titrated to effect (mean = 7.3 ± 5.5 U/kg)	To hospital discharge	Not defined/ measured	Reoperation (*P* Value = 0.013) FEIBA = 8.0% No FEIBA = 3.0% Thromboembolism (*P* Value = 0.48) FEIBA = 18.0% No FEIBA = 16.0% Mortality at 30 days (*P* Value = 1.00) FEIBA = 6.0% No FEIBA = 6.0%
Peksa *et al.* (2020)[25]	VKA reversal	Retrospective, multicenter, propensity score–matched analysis	Warfarin-associated major hemorrhage (FEIBA N = 86/4F-PCC N = 86)	500 U (INR < 5.0) 1,000 U (INR ≥ 5.0)	To hospital discharge (FEIBA median = 5.1 days)	Not defined/ measured	Achieved INR ≤ 1.5 FEIBA = 70.9% *vs.* 4F-PCC = 88.4% 95% CI difference, –29.2% to –5.7% Thromboembolism (*P* = n.s.) FEIBA = 5.8% 4F-PCC = 7.0% Mortality (*P* = n.s.) FEIBA = 26.7% 4F-PCC = 18.6%
Schulman *et al.* (2017)[26]	DOAC-related bleeding	Prospective, multicenter, observational cohort study	DOAC-associated major bleeding (N = 14)	50 U/kg	30 ± 2 days	Criteria as defined by Sarode *et al.*[27]	Effective hemostasis Good = 64% [95% CI, 35 to 87] Thromboembolism = 0% Death = 7.1% (1 of 14)
Shaw *et al.* (2020)[28]	DOAC-related bleeding	Retrospective single-center review	DOAC-associated bleeding (N = 54) + preoperative optimization of hemostasis (N = 28)	25–50 U/kg	30 days	ISTH criteria for effective hemostasis	ISTH effective hemostasis = 50% Surgical hemostasis "normal" = 84% Thromboembolism = 6.1% Mortality = 31.7%

4F-PCC, four-factor PCC; DOAC, direct oral anticoagulant; FEIBA, factor eight inhibitor bypassing activity; INR, international normalized ratio; SURF, SURgical interventions with FEIBA; VKA, vitamin K antagonist.

are patients presenting with hemorrhage in the setting of anticoagulant therapy. Four-factor PCC carries an FDA approval for the reversal of vitamin K antagonists (VKAs; *e.g.*, warfarin) either in the context of major bleeding or in patients needing an urgent surgery/invasive procedure. Four-factor PCC demonstrates superiority over plasma transfusion in both speed of international normalized ratio (INR) correction and clinical hemostasis.[27,32] From a mechanistic standpoint, four-factor PCC rapidly and adequately corrects the deficiency of vitamin K–dependent coagulation factors (II, VII, IX, X) that are depleted in the context VKA therapy.[32] The added benefit of using an activated coagulation factor concentrate such as FEIBA in this setting is uncertain and might carry excess risk relative to four-factor PCC. Indeed, the off-label use of FEIBA for VKA reversal has been limited due to concerns of increased thrombotic risk related to the inclusion of FVIIa compared to the nonactivated FVII in PCC. However, some centers might use FEIBA for VKA reversal to maintain a narrow medication formulary, or to reduced costs by using conservative FEIBA dosing, and FEIBA may be administered to patients with a history of heparin-induced thrombocytopenia, whereas most four-factor PCC formulations contain small amounts of heparin.[25] A single-center retrospective study of patients presenting with warfarin-associated intracerebral hemorrhage (ICH) and receiving FEIBA (15 or 25 U/kg based on admission

INR) found that FEIBA resulted in significantly faster INR correction compared to plasma, and thrombotic events were comparable between the two groups.[33] A retrospective multicenter matched case-control study comparing high-dose, weight-based FEIBA (50 U/kg; median dose, 4,530 U) *versus* plasma for the treatment of life-threatening bleeding also found that FEIBA resulted in significantly faster INR reversal, while the risk of thromboembolic events was similar between the groups.[34] A prospective observational study of patients presenting with major bleeding and VKA-associated coagulopathy (INR greater than 1.5) who received a fixed low dose of FEIBA for VKA reversal (500 U for INR less than 5.0 or 1,000 U for INR 5.0 or greater) demonstrated effective INR correction (93%), but a risk of thromboembolism of 14%.[35] Similarly, two retrospective studies comparing fixed low-dose FEIBA *versus* four-factor PCC for VKA reversal observed that four-factor PCC achieved the target INR of 1.5 or less in a greater portion of treated patients than FEIBA (table 2).[25,36] A third study found no difference in the ability of fixed low-dose FEIBA and four-factor PCC (dosed according to the FDA-approved dosing algorithm) to achieve a posttreatment INR less than 1.4 within 24 h (adjusted odds ratio, 1.4; $P = 0.44$).[37] These small retrospective studies indicate that a low fixed dose of FEIBA (500 to 1,000 U) seems to be associated with comparable thromboembolic risk to standard weight- and INR-based dosing of four-factor PCC. Importantly, the data highlighted above are drawn exclusively from patients receiving FEIBA for major bleeding, and most of these studies excluded patients needing VKA reversal for urgent surgery.[25,36,37] Taken together, these data suggest that FEIBA could be considered an acceptable alternative for VKA reversal at centers where four-factor PCC is otherwise unavailable and rapid INR reversal is needed, as is often the case in a perioperative setting. On the other hand, there are few data from either a mechanistic or empirical standpoint to suggest that FEIBA necessarily confers a hemostatic benefit over four-factor PCC in the context of VKA reversal.

Direct Oral Anticoagulants

Patients on direct oral anticoagulants (DOACs), including dabigatran, a direct thrombin inhibitor, and direct FXa inhibitors, such as rivaroxaban and apixaban, are increasingly encountered in the perioperative setting and can present with hemorrhage or require emergent surgical procedures necessitating reversal of anticoagulation. Evidence supporting the use of FEIBA for DOAC-associated bleeding stems primarily from *in vitro* data and animal studies.[38,39] PCCs and aPCCs were first proposed as potential DOAC "reversal agents" by Van Ryn *et al.* in 2008[40] and first evaluated *in vivo* in 2011 by Eerenberg *et al.*[41] Marlu *et al.* compared the *in vitro* hemostatic activity of PCC, aPCC, and rFVIIa using several modalities, including TGAs.[42] They found that PCC was able to correct quantitative parameters of thrombin generation in the presence of DOAC anticoagulation, and rFVIIa was able to correct kinetic parameters of thrombin generation, but only FEIBA was able to correct both quantitative and kinetic parameters of thrombin generation. Subsequently, Martin *et al.* demonstrated that aPCC added to apixaban-spiked whole blood was better able to restore clot structure, fibrin polymerization kinetics, and thrombin generation parameters as compared to PCC.[43] More recently, Rayatdoost *et al.* were able to demonstrate using an *in vitro* spiking study that both FEIBA and four-factor PCCs corrected rivaroxaban-induced suppression of peak thrombin generation and the endogenous thrombin potential.[44] FEIBA consistently and significantly shortened rivaroxaban-induced lag time prolongation, whereas four-factor PCC's effects were inconsistent or negligible. Four-factor PCC prohemostatic effects were absent at higher rivaroxaban concentrations (150 ng/ml or greater).

In vivo human experience with FEIBA for DOAC-associated bleeding is sparse and mostly limited to retrospective case studies. A prospective case-series reported that FEIBA at a dose of 50 U/kg prevented hematoma expansion in five DOAC-treated patients presenting with ICH, with no observed thrombotic complications.[45] A subsequent retrospective chart review of 11 FXa inhibitor-treated patients presenting with ICH found that the administration of 20 U/kg FEIBA resulted in hematoma stabilization in 55% of patients, while 36% showed worsening hemorrhage.[46] Low (less than 20 U/kg) and moderate (20 to 30 U/kg) FEIBA doses were compared for treatment of DOAC-related major bleeding in a later retrospective study.[47] Hemostasis was achieved in the majority of patients in both groups, although 9% of patients required an additional dose, two thirds of whom were in the low-dose group. Thrombotic complications were observed in 8% of patients and included deep vein thrombosis (DVT) and pulmonary embolism. Importantly, these retrospective studies used *ad hoc* study-specific definitions of effective hemostasis, based on either a lack of hematoma progression on imaging or based on a subjective evaluation by the care provider.

One small multicenter prospective observational study (n = 14) evaluated the hemostatic efficacy of FEIBA for dabigatran-associated bleeding (table 2).[26] Patients received FEIBA at a weight-based dose of 50 U/kg (median dose, 4,099 U), and hemostatic efficacy was rated as good in 64% and moderate in 36% of cases, respectively. There were no thromboembolic events. A more recent single-center, retrospective study evaluated the use of FEIBA for DOAC-associated bleeding, or for optimization of hemostasis before urgent surgery.[28] Eighty-two patients were included, 54 of whom received FEIBA for major bleeding, and 28 received FEIBA for an urgent surgical intervention. Hemostasis was effective (based on International Society on Thrombosis and Haemostasis [Carrboro, North Carolina] criteria)[48] in 50% of patients who received FEIBA for major bleeding, whereas surgical hemostasis was normal in 84% of patients receiving FEIBA for urgent surgery. The 30-day risk of thromboembolism was 6.1%.

Since these studies were performed, agent-specific reversal agents have been introduced, namely idarucizumab for dabigatran and andexanet alfa for FXa-inhibitors.[49,50] Idarucizumab was studied in patients with major bleeding, or before urgent surgery, and is approved for use in both of these indications. Andexanet alfa is currently only approved for the reversal of apixaban/rivaroxaban in the setting of life-threatening bleeding. Importantly, andexanet alfa has not been approved for FXa inhibitor reversal before urgent surgery, and trials are ongoing in this patient population. Andexanet alfa may not be available in all healthcare settings due to cost, and there is uncertainty surrounding potential thromboembolic risk.[51,52] Furthermore, there are concerns that andexanet alfa can interact with heparin-bound antithrombin, resulting in partial heparin reversal and heparin resistance. This becomes important for patients receiving andexanet alfa for FXa inhibitor reversal before urgent cardiac surgery, where heparin resistance can delay the implementation of cardiopulmonary bypass (CPB) and increase the risk of circuit thrombosis.[51,53,54]

There are no *in vivo* data directly comparing the clinical hemostatic efficacy of FEIBA with that of specific reversal agents, either in the context of major bleeding or for urgent surgical procedures. Among the available nonspecific hemostatic agents (four-factor PCC, rFVIIa, FEIBA), *in vitro* studies using TGAs do suggest that aPCC might confer an optimal hemostatic effect.[39,42,43] On the other hand, it is important to highlight that FEIBA is not a true "reversal agent." PCCs likely achieve a hemostatic effect through a bypassing mechanism where anticoagulant effects are overcome by increasing coagulation factor levels.[55] Four-factor PCC does not reduce circulating DOAC levels, and this is likely to similarly be the case for FEIBA.[52,56,57]

Cardiac Surgery

Another patient population that can experience uncontrolled bleeding are patients undergoing cardiac surgery, where anticoagulant use, hemodilution, and blood vessel damage can all contribute to hemorrhage refractory to blood product transfusion. Consequently, there is increasing off-label use of FEIBA to control severe perioperative hemorrhage during cardiac surgery.[58] Early retrospective studies assessing the effect of FEIBA administration as rescue therapy for refractory blood loss during complex cardiac procedures including aortic surgery, combined valve/coronary artery bypass grafting procedures, left ventricular assist device implantation, and heart transplantation demonstrated a decrease in transfusion requirements as well as chest tube output.[59,60] The majority of patients received a single dose either intraoperatively or postoperatively with average doses ranging from 1,225 to 2,154 U per patient. Thrombotic adverse events included the development of a clotted hemothorax, renal failure requiring hemodialysis, distal extremity ischemia, and an upper extremity DVT. Attributing these to FEIBA administration was not possible due to the small size and retrospective nature of the studies. A retrospective, propensity-matched study of 378 patients undergoing isolated on-pump coronary artery bypass grafting observed no significant difference in 30-day mortality between the FEIBA (n = 63) and non-FEIBA groups (n = 315; table 2). The FEIBA group received 500 U initially, with an additional 500 U if significant bleeding persisted (average dose, 9.7 U/kg), and thrombotic complications, including stroke, DVT, and pulmonary embolism, were comparable between groups.[23] An additional propensity-matched, retrospective analysis of patients undergoing type A aortic dissection repair demonstrated that administration of 500 to 1,000 U FEIBA significantly reduced postoperative transfusion requirements for red blood cells, platelets, plasma, and cryoprecipitate in the first 48 h after surgery without increasing the risk of thrombotic complications.[61] Use of 500 to 1,000 U FEIBA (dose based on degree of microvascular bleeding) as a first-line treatment for postbypass coagulopathy was also compared to plasma transfusion in a retrospective, propensity-matched, observational study that demonstrated a decrease in overall transfusion requirements, reduced postoperative ventilation times, shorter intensive care unit stays, and lower 30-day readmission rates.[62] More recently, a retrospective, propensity-matched analysis of 704 adult patients undergoing cardiac surgery on CPB (excluding transplants and procedures for ventricular assist devices) observed that low-dose FEIBA, dosed in 250-U increments (mean dose, 7.3 ± 5.5 U/kg), did not increase thromboembolic event risk, intensive care unit length of stay, or mortality. However, higher doses were associated with increased acute renal failure and postoperative transfusion (table 2).[24]

Pediatric Cardiac Surgery

FEIBA has also been investigated as rescue therapy for excessive bleeding during pediatric cardiac surgery. *Ex vivo* studies demonstrated that the addition of FEIBA to neonatal plasma sampled after CPB decreased thrombin generation lag time (the time for thrombin generation to first occur), as well as augmented the peak and rate of thrombin generation.[63] Furthermore, the addition of FEIBA to post-CPB plasma reduced clot degradation rates and restored neonatal fibrin network properties more effectively than cryoprecipitate.

Subsequent studies focused on intraoperative FEIBA use and efficacy in reducing transfusion requirements. A retrospective study of neonatal patients (defined as postnatal age less than 30 days) undergoing cardiac surgery with CPB found that FEIBA administration (initial dose, 10 U/kg; mean dose, 15.5 U/kg) resulted in a decrease in transfusion requirements compared to propensity-matched controls without increases in postoperative thromboembolic events at 7 or 30 days.[64] Another study assessed the use of FEIBA in 5-U/kg doses up to a maximum of 15 U/kg in pediatric patients 15 kg or less undergoing cardiac operations with

CPB, 25% of whom were newborns and 43% of whom had cyanotic disease.[65] The authors found no difference in total transfusion volumes compared to propensity-matched controls, although the FEIBA group did receive a lower volume of red blood cell transfusion after CPB and arrived in the intensive care unit with higher hemoglobin concentrations and lower INR values.

It is important to recognize, however, that the current evidence for use of FEIBA in cardiac surgery is based on retrospective, single-center studies and is therefore subject to sampling bias, incomplete outcome capture, and smaller patient populations limiting the generalizability of their findings. Prospective, randomized, controlled trials are needed to definitively demonstrate safety and efficacy in this population.

Safety

Given the relatively high concentration of prothrombin in FEIBA and its longer half-life (60 to 72 h) compared to the other included coagulation factors (6 to 24 h), large and repeated doses can result in an increased risk of thrombosis.[30,66] According to the FEIBA package insert, there is a boxed warning regarding the risk of thromboembolic events, including disseminated intravascular coagulation, venous thrombosis, pulmonary embolism, myocardial infarction, and stroke.[30] These concerns stem from reports of serious thromboembolic events among relatively young patients with hemophilia who would not otherwise have been expected to experience thromboembolic complications.[67–69] Most of these events occurred after very high doses of FEIBA over the course of several days, which is typical for its use in patients with hemophilia. These doses are well beyond those proposed for the management of refractory bleeding. Such events have been reported in both clinical trials and postmarketing surveillance, emphasizing the need for vigilance when using FEIBA, especially in surgical settings. Among patients with hemophilia and inhibitor antibodies, the incidence of thrombotic events after FEIBA administration was found to be 4.05 per 100,000 infusions, with the most significant contributor being doses exceeding 200 U · kg^{-1} · day^{-1}, which occurred in 50% of cases.[66] This compares to a rate of 0.17% for rFVIIa when used for all approved indications[70] and 0.01% for four-factor PCC when used for VKA reversal.[71]

Off-label use of FEIBA for refractory bleeding in patients without inhibitor antibodies may result in supraphysiologic levels of thrombin, potentially overwhelming natural anticoagulant mechanisms. This imbalance can precipitate thrombotic events, especially in patients with predisposing risk factors such as obesity, prolonged immobilization, or a history of thrombosis. In surgical patients, additional procoagulant stimuli from tissue injury and inflammatory mediators can amplify thrombin generation, increasing the risk of thrombotic complications.[72,73] The added thrombotic risk directly attributable to FEIBA administration during cardiac surgery has been challenging to estimate due to nonrandomized study designs, small sample sizes, variable FEIBA dosing strategies, and likely high baseline thrombotic risk in an otherwise comorbid population of cardiovascular patients. A systematic review identified two case series, two retrospective cohort studies, and one small pilot randomized controlled trial. This review estimated that the rate of thromboembolic complications from FEIBA use in cardiac surgery was 4.6%, although thromboembolic risk could be higher with real-world use.[74]

Since then, retrospective, propensity-matched analyses evaluating the administration of 500 to 1,000 U of FEIBA for refractory bleeding during coronary artery bypass grafting and type A aortic dissection repair did not demonstrate a significant difference in thrombotic events compared to patients who did not receive FEIBA (table 2).[23,61] FEIBA use to treat hemorrhage after left ventricular assist device implantation (average dose, 992 U or approximately 13 U/kg) found a nonsignificant difference in the incidence of thrombotic events in the FEIBA cohort compared to a control cohort (11.0% *vs.* 7.6%, respectively).[75] Furthermore, the study investigating use of 500 to 1,000 U FEIBA in lieu of plasma transfusion during cardiac surgery also found no statistical difference in rates of stroke or need for coronary reintervention.[62] Similarly, retrospective studies assessing FEIBA use in pediatric cardiac surgery have not demonstrated increased rates of thrombosis when compared to propensity-matched controls,[65] including when doses exceeded 20 U/kg.[64] The previously mentioned propensity-matched analysis by Nicholas *et al*. included 352 patients receiving an average FEIBA dose of 7.3 ± 5.5 U/kg during cardiac surgery and found no statistically significant difference in the odds ratio for thromboembolic outcomes when compared to the propensity-matched cohort (table 2).[24] Unfortunately, all of these studies are limited in their ability to fully assess the safety of FEIBA due to their retrospective nature and the absence of comprehensive surveillance for thrombotic events.

Dosing and Monitoring

Weight-based dosing for patients with hemophilia and inhibitors ranges from 50 to 100 U/kg, typically repeated at 6- to 12-h intervals (maximum daily dose, 200 U/kg) and continued for several days after surgery to preserve adequate postoperative hemostasis.[22] This intensive strategy is needed due to the persistent nature of factor inhibitors in patients with hemophilia. This is in contrast to the lower dosing reported when FEIBA is used for off-label indications, such as after cardiac surgery, or for anticoagulant-related bleeding. A single dose is typically used for these indications, with consideration of a repeat dose if hemostasis remains inadequate. The dosing reported in the few studies where FEIBA was used *in vivo* for DOAC-associated bleeding ranged from

25 to 50 U/kg.[26,28] For postoperative bleeding after cardiac surgery, dosing generally ranged from fixed doses of 250 to 2,000 U,[23,24,61] or weight-based dosing of 10 to 20 U/kg.[64,65]

Due to the complexity of FEIBA's mechanism of action and variability in response, reliable laboratory tests for monitoring its effect are lacking, and no validated assay is currently available. Dosing is adjusted based on clinical response (*e.g.*, visual inspection, hemoglobin trends) rather than specific coagulation laboratory monitoring. Even among patients with hemophilia and inhibitors, for which the most clinical experience is available, monitoring and repeat dosing are largely based on a clinical assessment of hemostasis.

Conventional coagulation assays (*e.g.*, prothrombin time, activated partial thromboplastin time) do not provide a physiologically relevant measure of *in vivo* thrombin generation and cannot measure the full effects of FEIBA on coagulation.[7,9,12,76] Furthermore, these tests do not account for cellular contributions to hemostasis and therefore are not useful for monitoring the *in vivo* effects of FEIBA treatment. Viscoelastic methods, such as rotational thromboelastometry (ROTEM) and thromboelastography, simultaneously measure clot formation kinetics (*i.e.*, coagulation activation), clot strength (contribution of platelets and fibrinogen), and fibrinolysis. Viscoelastic testing is usually performed using whole blood, at the point of care, and with a rapid turnaround time. For these reasons, ROTEM and thromboelastography may be useful for monitoring perioperative FEIBA therapy. Viscoelastic methods have shown promise in guiding the treatment of hemophilia patients with inhibitors.[77,78] However, their utility in patients receiving hemostatic therapies for life-threatening bleeding in a surgical setting requires further study. Limited data are available to inform what changes would be expected from FEIBA administration in patients having cardiac surgery. Most data are derived from patients with hemophilia and inhibitors, *in vitro* DOAC spiking experiments, or *in vitro* models of dilutional coagulopathy.[43,78–80] These studies suggest that FEIBA administration would be expected to partially improve both clot kinetic measures (*e.g.*, ROTEM clotting time and clot formation time) and clot firmness (*e.g.*, ROTEM maximum clot firmness). Elvstam *et al.* were able to demonstrate using ROTEM and an *in vitro* model of dilutional coagulopathy that FEIBA overcorrected the ROTEM clotting time, normalized the clot formation time, and partially improved both the alpha angle and maximum clot firmness.[80] In this study, PCC paradoxically prolonged the clotting time and clot formation time and negatively affected the alpha angle and maximum clot firmness. This effect was attributed to the heparin contained in PCC and was partially mitigated by pretreating samples with protamine.

TGAs have been applied in a clinical context toward measuring the pharmacodynamic effects of bypassing therapy in patients with hemophilia and inhibitors,[81] as well as in a research context for measuring the pharmacodynamic impact of nonspecific hemostatic therapy in patients with DOAC-associated bleeding.[39,82,83] While TGAs might be best suited to measure the *in vivo* effects of complex multicomponent coagulation factor concentrates, technical complexity, longer turnaround times, and a lack of knowledge on how to best use the results to guide therapy might limit their use in an applied clinical setting, at least in the near term. Further research and validation are needed to learn the best way this technology can be used to monitor and tailor the use of hemostatic therapies when applied toward off-label indications. Guidelines on the standardized application of TGAs are now available and might help shape future implementation efforts at the bedside.[11,84]

Both viscoelastic methods and TGAs might prove useful to measure the net pharmacodynamic effect of FEIBA's multimodal mechanism of action. Currently, their use at the bedside is limited, and more research is needed to better understand how clinicians can best leverage their potential for clinical decision-making in this context. For the time being, clinical evaluation and an individualized assessment of hemostasis remain the mainstay to monitor FEIBA's hemostatic effect. Clinical vigilance and appropriate dose selection are key, and physicians should pay close attention for signs and symptoms of thromboembolic complications in the weeks after FEIBA administration.

Conclusions

FEIBA has proven to be a valuable therapeutic option for managing refractory perioperative bleeding, particularly in patients with hemophilia A or B who have developed inhibitory antibodies against FVIII or FIX. FEIBA might also represent a promising treatment modality for patients experiencing refractory DOAC-associated bleeding. The off-label use of FEIBA in cardiac surgery has shown encouraging results in reducing transfusion requirements and improving hemostatic outcomes. However, the associated risk of thromboembolic events due to its procoagulant properties necessitates cautious application. Careful patient selection, adherence to dosing guidelines, and vigilant monitoring are essential to mitigate these risks. While conventional coagulation testing is not suitable for monitoring FEIBA's effects, viscoelastic methods and TGAs might be promising methods to better identify patients who stand to benefit from FEIBA. Limited data based on retrospective studies with variable dosing strategies also make development of algorithms for the perioperative use of FEIBA challenging. Prospective, randomized trials are needed to standardize dosing, define appropriate laboratory monitoring protocols, and fully elucidate FEIBA's safety profile in diverse and high-risk surgical populations, particularly in adult and pediatric cardiac surgery where off-label use is increasing.

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Competing Interests

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