Factor eight inhibitor bypassing activity for refractory bleeding in coronary artery bypass grafting: A propensity-matched analysis

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Abstract

Background: Perioperative bleeding and transfusion have been associated with major morbidity and mortality after cardiac surgery. As concerns remain regarding potential graft thrombosis following administration of a prothrombin factor concentrate, the use of factor eight inhibitor bypassing activity (FEIBA) in managing refractory postoperative bleeding has never been evaluated in patients undergoing isolated coronary artery bypass grafting (CABG).

Objectives: We aimed to examine the safety of FEIBA in patients undergoing isolated CABG, with respect to 30-day mortality, perioperative outcomes, and thrombotic complications.

Methods: A retrospective review was undertaken of all consecutive patients who had undergone isolated on-pump CABG between January 2015 and December 2019 at North Shore University Hospital. Patients requiring intraoperative extracorporeal membrane oxygenator support were excluded. Patients were divided into two groups, dependent upon whether they received FEIBA (n = 63) versus no FEIBA (n = 2493). A 1:5 propensity match analysis was employed, and patients were analyzed with respect to thrombotic complications, reintervention for myocardial ischemia, and short-term clinical outcomes.

Results: There was no difference in 30-day mortality between the two cohorts. There was also no significant difference in a composite of thrombotic complications (composed of deep vein thrombosis, pulmonary embolism, and stroke) between the two groups. Similarly, there was no significant difference in the requirement for postoperative reintervention for myocardial ischemia between patients who received FEIBA versus those who did not.

Conclusions: Factor eight inhibitor bypassing activity may be safe when used as rescue therapy for refractory bleeding following isolated CABG.
1 | INTRODUCTION

Coagulopathic-induced bleeding that is refractory to conventional treatment is a well-established cause of major morbidity and mortality in cardiac surgery.\(^1\)\(^-\)\(^4\) Patients undergoing coronary artery bypass grafting (CABG) following acute coronary syndrome are at higher risk of bleeding, as these patients are often treated with dual antiplatelet therapy.\(^5\)\(^-\)\(^6\) When postoperative coagulopathic bleeding is encountered, current treatment strategies aim to correct platelet and coagulation factor deficiencies, frequently with large-volume transfusion. These treatments are often ineffective and carry an inherent risk. When postoperative bleeding remains refractory to standard treatment, alternative hemostatic modalities are needed.

Recent years have seen the gradually increasing use of prothrombin complex concentrates (PCCs) in cardiac surgery, largely as salvage therapy to treat refractory bleeding. There have been several reports attesting to the efficacy of recombinant activated factor VII (FVIIa), there is a paucity of data regarding the use of FEIBA for refractory postoperative bleeding. Most data emanate from FEIBA's use in managing hemophilia and reversal of warfarin anti-coagulation.\(^7\)\(^-\)\(^9\) In contrast to the abundance of literature focused on activated factor VII (FVIIa), there is a paucity of data regarding the use of FEIBA for refractory postoperative bleeding. Most data emanate from FEIBA's use in managing hemophilia and reversal of warfarin anti-coagulation.\(^10\)\(^-\)\(^11\) There is, however, little information available regarding its safety in the patient undergoing coagulopathic cardiac surgery. Moreover, likely owing to reports of thrombotic complications in PCCs and the potential for graft thrombosis,\(^9\)\(^,\)\(^12\)\(^-\)\(^15\) there are no data on the use of FEIBA in patients undergoing isolated CABG. Consequently, we sought to evaluate our experience in patients receiving FEIBA for refractory coagulopathy following isolated CABG.

2 | METHODS

2.1 | Study population and definitions

A retrospective review was undertaken of all patients who underwent isolated CABG, aged 18 years or older, between January 2015 and December 2019 at North Shore University Hospital. Patients who were done as off-pump CABG (104 patients) and patients who required intraoperative extracorporeal membrane oxygenator support (3 patients) were excluded. Patients were divided into two cohorts, dependent upon whether they received perioperative FEIBA or not.

This study was conducted with the approval of the Northwell Health Institutional Review Board (May 26, 2020; IRB approval 20-0457); consent was waived.

2.2 | Data analysis

Definitions of patient demographic characteristics, perioperative variables, and postoperative outcomes were obtained from the New York State Cardiac Surgery Reporting System (https://www.health.ny.gov/forms/cardiac_surgery) and from the Society of Thoracic Surgeons Adult Cardiac Surgery Database (http://www.sts.org/registries-research-center/sts-national-database/adult-cardiac-surgery-database/data-collection).

To detect a significant difference in a composite of mortality and thrombotic complications, a power analysis using a two-sided t test revealed a power of 0.803 with an alpha of 0.05.

Observed covariates at baseline were identified. To control for potential confounding influences, we calculated propensity scores (or the probability of assignment to the "FEIBA" or "No FEIBA" group) using multivariable logistic regression for each patient; variables with a p value <0.10 and those considered to have clinical relevance were weighted equally and subsequently included in the multivariable logistic regression model, which computed the propensity scores. The variables used in the final propensity score model were sex, age, diabetes mellitus, dialysis-dependent renal failure, cerebrovascular disease, chronic lung disease, peripheral vascular disease, incidence of surgery (e.g., first, second, third cardiac surgery), presurgical hemoglobin and platelet values, ejection fraction, presurgical presence of intra-aortic balloon pump, presurgical adenosine diphosphate (ADP) receptor inhibitor therapy, and surgical status (e.g., elective, urgent, emergent).

Patients who received FEIBA were matched with patients who did not in a 1:5 ratio through a nearest-neighbor-matching algorithm. To exclude bad matches, we instituted a maximum caliper of 0.10 or less of the standard deviation of the logit of the propensity score. The balance of the baseline covariates after propensity matching was assessed by examining the standardized difference of the mean, with a value less than 0.1 considered well balanced for each covariate. The area under the curve for the receiver operating characteristic of the propensity model was 0.78. The matched sample included a total of 378 patients, evenly distributed in a 1:5 ratio [63:315] between the FEIBA and No FEIBA groups (Figure 1).
Assumption of normality of continuous data was tested by the Kolmogorov–Smirnov and Shapiro–Wilk tests. If assumption of normality was met, continuous variables were compared using the Student t test, whereas the Mann-Whitney U test was used for nonparametric variables. Following propensity matching, comparisons in the propensity-matched pairs were performed using the Wilcoxon rank-sum test for continuous variables and McNemar’s test for binary data.

A p value less than 0.05 was considered as statistically significant. We used SAS 9.4 (SAS Institute) for all analysis. Results were considered statistically significant at p less than 0.05.

2.3 | Use of FEIBA

Our practice has been to administer FEIBA (Takeda Pharmaceuticals, Inc.) primarily as a salvage measure, following the transfusion of other blood products (including red blood cells [RBCs], platelets, plasma, and/or cryoprecipitate), in patients undergoing CABG who have persistent bleeding deemed coagulopathic in nature.

If significant bleeding persists that is deemed not surgically correctable following the administration of these more traditional blood products, FEIBA is then administered (500 units). While our institutional preference is to start with 1000 units for our nonisolated CABG cases, we have adopted a more conservative approach for initial concern with potential graft thrombosis in this patient population. If blood continues to pool in dependent locations in the pericardial well and/or the bleeding appears uncontrollable by gauze packing and/or surgical chest drains, an additional 500 units of FEIBA are further administered.

3 | RESULTS

3.1 | Patient demographics and operative data

Patient characteristics and clinical presentation are summarized in Table 1. There was a predominance of male patients, and the majority had a history of hypertension and dyslipidemia. Prior to matching, the FEIBA group had a significantly lower platelet count compared to the No FEIBA group (191.8 ± 88.7 vs. 225.8 ± 704.7; p < 0.001), greater incidence of preoperative use of ADP receptor inhibitors used within 5 days (30.2% vs. 12.5%; p < 0.001), a lower proportion of patients with elective cases (4.8% vs. 15.2%) and greater proportion of emergent cases (7.9% vs. 1.7%) when compared to the No FEIBA group.

After matching, there was no significant difference in preoperative hematocrit or platelet levels between groups. Similarly, there was no significant difference in the preoperative use of anticoagulation, aspirin, or ADP receptor inhibitors used within 5 days between groups. There were also no significant differences regarding left ventricular ejection fraction, preoperative inotropic support, incidence of intra-aortic balloon pump, status of the surgery (elective vs. urgent vs. emergent), and incidence of first-time cardiac surgery between cohorts.

Intraoperative data are summarized in Table 2. While aortic cross-clamp time did not significantly differ between patient groups before or after matching, the FEIBA group underwent significantly longer duration of cardiopulmonary bypass than did the No FEIBA group both prior to (120.6 ± 55.2 min vs. 101.6 ± 40.4; p = 0.009) and following matching (120.6 ± 55.2 min vs. 105.1 ± 40.4; p = 0.009).

Those patients who received FEIBA required significantly greater intraoperative transfusion of all types of blood product both before (RBCs [median 1 unit vs. 0; p < 0.001], platelets [1 vs. 0; p < 0.001], plasma [0 vs. 4; p < 0.001], cryoprecipitate [0 vs. 0; p < 0.001]) and after matching (RBCs [median 1 units vs. 0; p < 0.001], platelets [1 vs. 0; p < 0.001], plasma [0 vs. 4; p < 0.001], cryoprecipitate [0 vs. 0; p < 0.001]).

The average dose was 9.7 units per kilogram of FEIBA per patient in the FEIBA group.

3.2 | Clinical outcomes

A summary of short-term outcomes is outlined in Table 3.

Overall, there were three deaths (0.8%), with no significant difference in 30-day mortality between the matched patient cohorts.

FIGURE 1  Patient flow diagram.
FEIBA, factor eight inhibitor bypassing activity; ECMO, extracorporeal membrane oxygenation; FEIBA, factor eight inhibitor bypassing activity.
There was also no significant difference in a composite of thrombotic complications (composed of deep vein thrombosis [DVT], pulmonary embolism, and stroke) between the two groups. Similarly, there was no significant difference in the requirement for postoperative reintervention for myocardial ischemia.

Duration of intensive care unit (ICU) stay (132.0 ± 202.7 h vs. 78.5 ± 115.6; p = 0.004) and overall length of hospitalization (12.4 ± 13.2 days vs. 9.23 ± 11.16; p = 0.05) were significantly longer in the FEIBA group. While not reaching statistical significance, there was a trend toward longer duration of postoperative mechanical ventilation requirement in the FEIBA group (64.4 ± 148.4 h vs. 31.2 ± 182.7; p = 0.16).

## DISCUSSION

The present study shows that the use of FEIBA as salvage therapy for refractory bleeding in isolated CABG is safe regarding mortality, thrombotic complications (DVT, stroke, myocardial infarction) and perioperative outcomes. To the best of our knowledge, this is the only study reporting on the use of FEIBA in isolated CABG. One of the vital questions with regard to FEIBA as a hemostatic adjunct in cardiac surgery is whether it is being used appropriately. Current guidelines state that in patients in whom bleeding is related to coagulation factor deficiency, PCC administration should be used to reduce both bleeding and transfusions and may be preferred over plasma when rapid normalization of coagulation factors is needed. However, this is without any explicit recommendations with regard to activated PCCs or FEIBA. Consequently, it seems reasonable that the off-label use of FEIBA be limited to cases in which intractable blood loss is not managed by conventional treatment, a setting that is estimated to occur in only 2% of cardiac cases. As such, our study used FEIBA in only 2.5% of our isolated CABGs. This finding was similar to Karkouti and colleagues, who showed in their large national observational study that none of the centers (which represents approximately 90% of the adult cardiac surgical volume in Canada) used recombinant factor VIIa (rFVIIa) in more than 2% of their cases. To date, no randomized clinical trials have assessed the efficacy of FEIBA in cardiac or other surgical settings. In fact, there are only two observational studies on the use of FEIBA in patients undergoing cardiac surgery at the writing of this manuscript. In their study of 25 patients undergoing surgery for aortic root replacement (Bentall or valve-sparing procedure) and heart transplant, Song et al. reported that the need for fresh frozen plasma and platelet transfusion decreased significantly after FEIBA administration. Likewise, Balsam

| Variable                        | All patients | Propensity-matched patients |
|---------------------------------|--------------|-----------------------------|
|                                 | FEIBA (n = 63) | No FEIBA (n = 2493)         | FEIBA (n = 63) | No FEIBA (n = 315) |
| **Age, years**                  |              |                             |              |                   |
|                                 | 67.6 ± 12.0  | 65.8 ± 10.1 0.16            | 67.6 ± 12.0  | 66.7 ± 10.5 0.55  |
| **Female sex**                  | 15 (23.8)    | 556 (22.3) 0.78             | 15 (23.8)    | 79 (25.1) 0.83   |
| **Hypertension**                | 58 (92.1)    | 2205 (88.4) 0.59            | 58 (92.1)    | 290 (92.1) >0.99 |
| **Dyslipidemia**                | 62 (98.4)    | 2369 (95.0) 0.41            | 62 (98.4)    | 297 (94.3) 0.22  |
| **Diabetes mellitus**           | 33 (52.4)    | 1412 (56.6) 0.81            | 33 (52.4)    | 179 (56.8) 0.52  |
| **Peripheral arterial disease** | 6 (9.5)      | 252 (10.1) 0.88             | 6 (9.5)      | 30 (9.5) >0.99   |
| **Cerebrovascular disease**     | 15 (23.8)    | 506 (20.3) 0.54             | 15 (23.8)    | 72 (22.9) 0.87   |
| **Chronic lung disease**        | 11 (17.5)    | 418 (16.8) 0.88             | 11 (17.5)    | 54 (17.1) 0.86   |
| **Dialysis-dependent renal failure** | 3 (4.8)  | 108 (4.3) 0.76            | 3 (4.8)  | 16 (5.1) >0.99   |
| **Preoperative hematocrit**     | 38.9 ± 7.2   | 39.5 ± 5.9 0.48            | 38.9 ± 7.2   | 38.5 ± 6.8 0.65  |
| **Left ventricular ejection fraction (%)** | 49.2 ± 16.3 | 51.3 ± 15.0 0.26 | 49.2 ± 16.3 | 48.7 ± 16.7 0.82 |
| **Preoperative platelet count (K/μl)** | 192 ± 89 | 226 ± 705 <0.001  | 192 ± 89 | 191 ± 63 0.95 |
| **Preoperative ADP inhibitor**  | 30 (47.6)    | 776 (31.1) 0.02            | 30 (47.6)    | 163 (51.7) 0.55  |
| **Preoperative inotropic support** | 0 (0.0)  | 13 (0.5) 0.57            | 0 (0.0)  | 5 (1.6) 0.60   |
| **Preoperative IABP**           | 19 (30.2)    | 311 (12.5) <0.001          | 19 (30.2)    | 116 (36.8) 0.31  |
| **Surgical status**             |              |                             |              |                   |
| **Elective**                    | 3 (4.8)      | 380 (15.2) 0.02            | 3 (4.8)      | 13 (4.1) 0.82   |
| **Urgent**                      | 55 (87.3)    | 2071 (83.1) 0.37           | 55 (87.3)    | 287 (91.1) 0.35  |
| **Emergent**                    | 5 (7.9)      | 42 (1.7) <0.001            | 5 (7.9)      | 15 (4.8) 0.30   |
TABLE 2  Operative data

| Variable                                      | All patients                                                                 | Propensity-matched patients                                                                 |
|-----------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
|                                               | FEIBA (n = 63)                                                              | No FEIBA (n = 2493)                                                                         | FEIBA (n = 63)                                                              | No FEIBA (n = 315)                                                                         |
|                                               | P value                                                                      | p value                                      | P value                                                                      | p value                                      |
| Cardiopulmonary bypass time, min              | 120.6 ± 55.2                                                                | 101.6 ± 40.0                                 | 120.6 ± 55.2                                                                | 105.1 ± 40.4                                 | 0.009                                      | 0.32                                      |
| Aortic cross-clamp time, min                  | 71.2 ± 36.8                                                                 | 66.4 ± 31.7                                 | 71.2 ± 36.8                                                                 | 69.1 ± 32.7                                 | 0.65                                       | 0.06                                      |
| First cardiovascular surgery                  | 61 (96.8)                                                                   | 2463 (98.8)                                 | 61 (96.8)                                                                   | 305 (96.8)                                 | >0.99                                      | <0.001                                    |
| First reoperative cardiovascular surgery       | 2 (3.2)                                                                     | 27 (1.1)                                    | 2 (3.2)                                                                     | 10 (3.2)                                    | >0.99                                      | <0.001                                    |
| Second reoperative cardiovascular surgery      | 0 (0.0)                                                                     | 3 (0.1)                                     | 0 (0.0)                                                                     | 0 (0.0)                                     | —                                          | —                                         |
| Intraoperative IABP                           | 5 (7.9)                                                                     | 65 (2.6)                                    | 5 (7.9)                                                                     | 11 (3.5)                                    | 0.11                                       | 0.26                                      |
| Intraoperative blood product usage            |                                                                              |                                              |                                                                              |                                              |                                              |                                           |
| Packed red blood cells, median (IQR)          | 1 (0 to 3)                                                                  | 0 (0 to 1)                                  | 1 (0 to 3)                                                                  | 0 (0 to 2)                                  | <0.001                                     | 0.55                                      |
| Platelets, median (IQR)                       | 1 (0 to 2)                                                                  | 0 (0 to 0)                                  | 1 (0 to 2)                                                                  | 0 (0 to 0)                                  | <0.001                                     | 0.81                                      |
| Plasma, median (IQR)                          | 0 (0 to 0)                                                                  | 0 (0 to 0)                                  | 0 (0 to 0)                                                                  | 0 (0 to 0)                                  | <0.001                                     | 0.52                                      |
| Cryoprecipitate, median (IQR)                 | 0 (0 to 1)                                                                  | 0 (0 to 0)                                  | 0 (0 to 1)                                                                  | 0 (0 to 0)                                  | <0.001                                     | 0.66                                      |

Note: Values are n (%) or mean ± standard deviation, unless otherwise specified.
Abbreviations: FEIBA, factor eight inhibiting bypassing activity; IABP, intra-aortic balloon pump; IQR, interquartile range; SMD, standardized mean difference.

TABLE 3  Clinical outcomes

| Variable                                      | All patients                                                                 | Propensity-matched patients                                                                 |
|-----------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
|                                               | FEIBA (n = 63)                                                              | No FEIBA (n = 2493)                                                                         | FEIBA (n = 63)                                                              | No FEIBA (n = 315)                                                                         |
|                                               | P value                                                                      | p value                                      | P value                                                                      | p value                                      |
| 30-day mortality                              | 1 (1.6)                                                                     | 19 (0.8)                                    | 1 (1.6)                                                                     | 2 (0.6)                                     | 0.42                                       | 0.09                                      |
| Composite of thrombotic complications         | 0 (0.0)                                                                     | 38 (1.5)                                    | 0 (0.0)                                                                     | 8 (2.5)                                     | 0.63                                       | 0.23                                      |
| Stroke                                        | 0 (0.0)                                                                     | 29 (1.2)                                    | 0 (0.0)                                                                     | 7 (2.2)                                     | 0.23                                       | 0.47                                      |
| Deep vein thrombosis                          | 0 (0.0)                                                                     | 8 (0.3)                                     | 0 (0.0)                                                                     | 0 (0.0)                                     | —                                          | —                                         |
| Pulmonary embolism                            | 0 (0.0)                                                                     | 1 (0.04)                                    | 0 (0.0)                                                                     | 1 (0.3)                                     | 0.65                                       | 0.08                                      |
| Reintervention for postoperative MI           | 0 (0.0)                                                                     | 5 (0.2)                                     | 0 (0.0)                                                                     | 0 (0.0)                                     | —                                          | —                                         |
| Reoperation for bleeding                      | 4 (6.3)                                                                     | 29 (1.2)                                    | 4 (6.3)                                                                     | 6 (1.9)                                     | 0.07                                       | 0.23                                      |
| Postoperative blood product usage             |                                                                              |                                              |                                                                              |                                              |                                              |                                           |
| Packed red blood cells, median (IQR)          | 3 (1–4)                                                                    | 0 (0–2)                                    | 3 (1–4)                                                                    | 1 (0–2)                                     | <0.001                                     | 0.78                                      |
| Platelets, median (IQR)                       | 0 (0–1)                                                                    | 0 (0–0)                                    | 0 (0–1)                                                                    | 0 (0–0)                                     | <0.001                                     | 0.63                                      |
| Plasma, median (IQR)                          | 0 (0–2)                                                                    | 0 (0–0)                                    | 0 (0–2)                                                                    | 0 (0–0)                                     | <0.001                                     | 0.81                                      |
| Cryoprecipitate, median (IQR)                 | 0 (0–1)                                                                    | 0 (0–0)                                    | 0 (0–1)                                                                    | 0 (0–0)                                     | <0.001                                     | 0.77                                      |
| Deep sternal wound infection                  | 0 (0.0)                                                                    | 4 (0.2)                                    | 0 (0.0)                                                                    | 0 (0.0)                                     | —                                          | —                                         |
| New-onset renal failure requiring dialysis    | 2 (3.2)                                                                    | 22 (0.9)                                   | 2 (3.2)                                                                    | 5 (1.6)                                     | 0.33                                       | 0.10                                      |
| Sepsis of any cause                           | 3 (4.8)                                                                    | 29 (1.2)                                   | 3 (4.8)                                                                    | 5 (1.6)                                     | 0.13                                       | 0.18                                      |
| Ventilation time, h                           | 64 ± 145                                                                   | 17 ± 102                                   | 64 ± 148                                                                   | 31 ± 183                                    | 0.16                                       | 0.20                                      |
| Duration of ICU care, h                       | 132 ± 203                                                                  | 58 ± 113                                   | 132 ± 203                                                                  | 79 ± 116                                    | 0.004                                      | 0.32                                      |
| Length of postoperative stay, days            | 12 ± 13                                                                    | 8 ± 8                                      | 12 ± 13                                                                    | 9 ± 11                                      | 0.05                                       | 0.26                                      |

Note: Values are n (%) or mean ± standard deviation, unless otherwise specified. Composite of thrombotic complications; composed of deep vein thrombosis, pulmonary embolism, and stroke.
Abbreviations: FEIBA, factor eight inhibiting bypassing activity; ICU, intensive care unit; IQR, interquartile range; MI, myocardial infarction; SMD, standardized mean difference.

et al. showed that blood product usage as well as hourly chest tube output were decreased significantly following the administration of FEIBA. As FEIBA is not currently approved for patients receiving cardiac surgery, it is used as a rescue treatment for those refractory to standard treatment; as such, decreased blood product usage was not an expected end point of our study. As only 2.5% of our entire
cohort received FEIBA, it is likely that its use represents a marker of a considerably sicker population of patients.

It is not surprising that patients who used FEIBA had higher intraoperative and postoperative blood product usage, as we use FEIBA as salvage, following the administration of other, more traditional blood products. Thus, it is likely that the longer duration of ICU stay, mechanical ventilatory requirements, and length of hospitalization can be attributed to the negative effects of bleeding and resultant increased intra- and postoperative transfusion requirements and the resulting volume load, and not the administration of FEIBA.

The safety profile of FEIBA as a hemostatic adjunct in the coagulopathic cardiac surgical patient is a significant and yet unaddressed issue. Local and systemic upregulation in the expression of tissue factor occurs following the administration of cardiopulmonary bypass. It has been hypothesized that this increased expression of tissue factor could result in the formation of both local and systemic clots, which would be exacerbated by hemostatic agents acting primarily on the intrinsic pathway of the coagulation cascade such as rFVIIa. It stands to reason that those patients undergoing CABG, with presumed unstable atherosclerotic disease in their native coronary vasculature, would be at further risk of perioperative ischemic events. A possible benefit of FEIBA may be its composition: a prothrombin complex concentrate that contains mainly nonactivated forms of factors II, IX, and X and small amounts of activated factor VII. Given its ability to work on both the extrinsic and intrinsic pathways of the coagulation cascade, FEIBA may provide a better safety profile as compared to rFVIIa. Song et al. postulated that given the ability to interact on both pathways, FEIBA could lead to the reduction in dosages necessary to reach therapeutic levels as compared to those needed for rFVIIa. They reported doses of 20 units/kg, which is only 20% of the dose recommended for its approved indication of hemophilia and 10% of the dose reported to cause increased thromboembolic events in patients with thrombotic risk factors. Similarly, we used an average dose of 9.7 units/kg per patient in our study. Song et al. reported one patient – with a central line and transvenous pacemaker – in their cohort who developed an upper extremity DVT. Balsam et al. found two thrombotic events in their cohort; one patient developed a clotted hemothorax, and the other suffered distal-extremity ischemia. However, as both these studies lacked a control group, it is not possible to determine causality. To the best of our knowledge, our study was the first to compare thrombotic complications and outcomes of patients undergoing CABG who required FEIBA to those who did not require FEIBA. We did not find any significant difference in a composite of thrombotic complications between the FEIBA and No FEIBA matched groups. Moreover, there were no episodes of postoperative myocardial ischemic events requiring intervention in either group.

A further advantage of FEIBA is that it may be administered (following reconstitution) in a volume of only 50 cc, whereas one unit of plasma is typically 200–250 cc, for example. This can be particularly advantageous in a complex CABG after long cardiopulmonary bypass and cross-clamp times, when one may be trying to limit the volume load on the right ventricle. Further, it may help to reduce the risk of circulatory overload and the transfusion-related acute lung injury that is associated with large-volume blood product administration.

5 | LIMITATIONS

While our results are encouraging, the findings of the present study should be viewed within the context of its inherent limitations. We were unable to account for race or ethnicity in our study, which is a limitation to understanding the sociocultural context of the studied population. This is a retrospective study with a small sample size. As there is no standardized protocol for the use of FEIBA in cardiac surgery, the dose, indication, and timing of FEIBA use was not standardized. We were unable to account for specific variations in transfusion volume already given to patients before the decision was made to use FEIBA, nor were we able to take into consideration differences in surgical technique between individual practitioners. Appropriately powered, randomized controlled clinical trials should be designed to determine the safety and efficacy of its use in cardiac surgery. Further, it would be beneficial to determine prospectively which patients undergoing CABG are at greatest risk for requiring FEIBA, such that it is used in more of a prophylactic role than as a rescue therapy. This would potentially allow for the decreased transfusion of blood and blood products and their associated adverse effects.

6 | CONCLUSION

This is the only study to date to systematically analyze the role of FEIBA in isolated CABG. Although there is no substitute for meticulous surgical technique, when used as rescue therapy for refractory bleeding after CABG, FEIBA appears safe and does not seem to be associated with increased adverse short-term events. In conclusion, the results of our study suggest that FEIBA may be considered for rescue therapy for refractory bleeding after CABG.

AUTHOR CONTRIBUTIONS

SSP and P-JY conceptualized and designed the research, collected data, and analyzed results. SSP drafted the initial article. MAC collected data and helped perform statistical analysis. SSP, P-JY, MAC, and ARH contributed to study design, reviewed and revised the manuscript, and approved the final article as submitted.

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RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest to report.

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