Factor VIII Inhibitor Bypass Activity and Recombinant Activated Factor VII in Cardiac Surgery

Vidya K. Rao, MD, MBA,* Robert L. Lobato, MD, MS,* Blake Bartlett, PharmD,† Mark Klanjac, PharmD,† Christina T. Mora-Mangano, MD,* P. David Soran, MD,* Daryl A. Oakes, MD,* Charles C. Hill, MD,* and Pieter J. van der Starre, MD, PhD*

Objective: **Postcardiopulmonary bypass hemorrhage remains a serious complication of cardiac surgery. Given concerns regarding adverse effects of blood product transfusion and limited efficacy of current antifibrinolytics, procoagulant medications, including recombinant factor VIIa (rFVIIa) and factor eight inhibitor bypass activity (FEIBA), increasingly have been used in managing refractory bleeding. While effective, these medications are associated with thromboembolic complications. This study compared the efficacy and risk of adverse events of rFVIIa and FEIBA in cardiac surgical patients with refractory bleeding.**

Design: **This retrospective study evaluated 168 patients who underwent cardiac surgery and received either FEIBA or rFVIIa to manage postbypass hemorrhage. Demographic, clinical, and outcomes data were collected and statistical analysis performed to compare thromboembolic event rates, relative efficacy, and 30-day mortality following administration of these medications.**

Setting: **Single university hospital.**

Participants: **Patients undergoing cardiac surgery.**

Interventions: **None.**

Measurements and Main Result: **Sixty-one patients received rFVIIa, and 107 received FEIBA. Demographics, surgical procedures, and preoperative anticoagulation were similar between the cohorts; however, the rFVIIa cohort had longer durations of cardiopulmonary bypass (305.1 *v* 243.8 min, $p < 0.01$). There were no significant differences in the number of thromboembolic events, 30-day mortality, or rates of revision surgery. Neither group demonstrated a clear relationship between dosage and occurrence of thromboembolic events. The rFVIIa cohort received more platelets than the FEIBA cohort (3.13 *v* 1.67 units, $p = 0.01$), but transfusion rates of other blood products were similar.**

Conclusions: **This study suggests that rFVIIa and FEIBA have similar efficacy and adverse event profiles in managing intractable postbypass hemorrhage in cardiac surgical patients. Further prospective studies are required.**

KEY WORDS: cardiac surgery, cardiac anesthesia, hemorrhage, hemostasis, transfusion, cardiopulmonary bypass, thromboembolic complications, coagulation, transfusion

POSTOPERATIVE HEMORRHAGE remains a potentially serious complication in patients undergoing cardiac surgical procedures requiring cardiopulmonary bypass (CPB). The incidence of excessive bleeding in cardiac surgery has been reported to be as high as 29%.[1]

Numerous factors contribute to the impairment of hemostasis after CPB, including residual heparinization, hypothermia, contact activation, inflammation, and fibrinolysis.[2,3] Historically, management strategies for postoperative hemorrhage have included allogeneic transfusion and the adjunctive administration of procoagulant medications, such as antifibrinolytics and desmopressin (DDAVP). However, massive transfusion is associated with potentially serious adverse effects; in particular, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), infection, and medical errors.[4–6] Studies evaluating antifibrinolytics and DDAVP reported variable efficacies of these medications in managing refractory hemorrhage.[7–10]

As a result, the off-label usage of recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk, Princeton, NJ) has been adopted to manage refractory bleeding. This procoagulant compound has been approved for the treatment of hemorrhage in patients with hemophilia A and B or factor VII deficiency. Recombinant factor VIIa functions by forming a complex with tissue factor (TF) and activated platelets to activate factors IX and X.[11–14] A procoagulant compound with similar indications, Factor Eight Inhibitor Bypass Activity (FEIBA, Baxter Healthcare, Deerfield, IL) has been used less widely. It is an activated prothrombin complex concentrate, containing prothrombin, nonactivated factors II, IX, and X, and activated factors II and VII.[15]

Although they are effective, both compounds notably have been associated with thromboembolic events, including stroke, myocardial infarction, pulmonary embolus, and intracardiac and major vessel thromboses.[16,17] Prior to the availability of rFVIIa in the authors' practice, FEIBA was the primary rescue therapy in cases of intractable post-CPB hemorrhage. They report their experiences with the use of FEIBA and rFVIIa in 168 cardiac surgical patients who developed refractory postoperative bleeding between 2005 and 2010.

MATERIALS AND METHODS

After obtaining approval from the institutional review board, a retrospective chart review was performed of adult patients who underwent cardiac surgical procedures between January 2005 and September 2010. Eligible patients were those over 18 years of age who underwent cardiothoracic surgery and received at least 1 dose of FEIBA or rFVIIa in the intraoperative or postoperative periods. Patients were excluded if they had a pre-existing diagnosis of hemophilia or underwent heart and/or lung transplantation.

The authors obtained demographic information, preoperative medical history, and pertinent clinical data from the perioperative period

*From the Departments of *Anesthesiology; and †Pharmacy, Stanford Hospital and Clinics, 300 Pasteur Drive, Stanford, CA.*

Address reprint requests to Vidya K. Rao, MD, MBA, Stanford Hospital and Clinics, Department of Anesthesia, Perioperative and Pain Medicine, 300 Pasteur Drive, Stanford, CA 94305. E-mail: vknayak@stanford.edu

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and hospital course for each of the identified patients. The primary outcome was the total number of thromboembolic events, defined as a composite endpoint including stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism observed during the first 30 postoperative days. Secondary outcomes included the number and type of blood products transfused postoperatively, the number of reoperations required to manage excessive bleeding, and 30-day mortality.

Intraoperative coagulation management was performed per institutional protocol. Baseline activated clotting time (ACT) and heparin response data were obtained for all patients prior to the administration of intraoperative anticoagulant medications. All patients received antifibrinolytic therapy in the form of aminocaproic acid as a 10-gram bolus dose followed by a 1 gram/hour infusion for approximately 10 hours. Prior to the institution of CPB, patients received an initial intravenous heparin bolus of 300 units/kg, with supplementary dosing as needed to achieve an ACT of >480 seconds. During CPB, additional heparin was titrated to maintain an ACT >480 seconds.

Post-CPB, heparin was reversed with adequate doses of protamine to achieve the patient's baseline ACT as well as a zero heparin concentration. Blood products, including packed red blood cells, fresh frozen plasma, platelets, and cryoprecipitate were administered at the discretion of the attending cardiothoracic surgeon and anesthesiologist. Select patients also received DDAVP at the discretion of the attending physicians. The Surgeries in this series were performed prior to the adoption of point-of-care testing, and, in most cases, no additional coagulation studies were obtained in the immediate post-CPB period prior to the arrival of the patient in the Cardiothoracic Intensive Care Unit (CTICU).

In refractory hemorrhage, defined as persistent microvascular bleeding deemed nonsurgical in nature despite conventional hemostatic efforts including protamine, antifibrinolytic therapy, and blood product transfusion, FEIBA or rFVIIa was administered after a consensus agreement between the attending surgeon and anesthesiologist. In the postoperative setting, the decision to administer FEIBA or rFVIIa was based on a similar consensus between the surgical and critical care attending physicians after evaluation of the patient's coagulation studies. Based on the severity of bleeding, the dosage of rFVIIa was approximated to either 45 μg/kg or 90 μg/kg. FEIBA was administered in either a low dose of 490 units, a moderate dose of approximately 600 units, or a high dose of 900-1,000 units. Both medications were administered over 10 to 15 minutes with careful hemodynamic monitoring and titration to effect based upon visual inspection of the surgical field and the chest tube output. Subsequent doses were administered as needed to achieve adequate hemostasis.

The decision to return to the operating room for re-exploration secondary to bleeding was made at the discretion of the surgical and CTICU teams based upon the rate and magnitude of chest tube output, laboratory evaluation of the coagulation profile, and the patient's overall hemodynamic status. General guidelines included chest tube output exceeding 400 mL/hour for 1 hour, 300 mL/hour for 2 hours, or 200 mL/hour for 4 hours in the setting of a corrected coagulation profile.

Statistical analysis was performed using R-version software 2.11.1. Discrete variables were analyzed using Pearson's chi-squared test, while continuous variables were analyzed using the Kruskal-Wallis test. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

Of the 2,619 cases performed between January 2005 and September 2010, 61 patients received rFVIIa, and 107 patients received FEIBA for the treatment of refractory bleeding in the post-CPB and postoperative periods. The baseline demographics of each group are presented in Table 1. There were no statistically significant differences between the 2 groups with regard to age, gender, or ethnicity.

Table 1. Baseline Demographics

	rFVIIa	FEIBA	p Value
Total Number of Patients	61	107	
Age (years)			
Mean ± SD	57.2 ± 15.1	60.5 ± 13.7	0.22
Median	59	60	
Gender			
Male	47 (77%)	74 (69%)	0.27
Female	14 (23%)	33 (31%)	
Ethnicity			
African-American	3 (5%)	10 (9%)	0.60
Asian	7 (11%)	18 (17%)	
Caucasian	40 (66%)	63 (59%)	
Hispanic	7 (11%)	8 (7%)	
Other	4 (7%)	8 (7%)	

NOTE. Values are n (%) unless otherwise indicated.

Abbreviations: FEIBA, Factor Eight Inhibitor Bypass Activity; rFVIIa, recombinant activated Factor VII; SD, standard deviation.

The majority of surgical procedures in both treatment groups were performed electively, with the most common procedures being an aortic root or arch repair with valve replacement (Table 2). Although a greater number of patients in the FEIBA group received warfarin in the preoperative period, there was no statistically significant difference between the cohorts with respect to preoperative anticoagulation. The groups did vary with regard to primary or revision surgery; the majority of patients in the FEIBA group underwent their first cardiac surgical procedure (64%) while the majority of patients in the rFVIIa group previously had undergone 1 or more operations (56%). All patients included in the study underwent procedures requiring CPB. The rFVIIa group was noted to have a statistically significantly longer duration of CPB time.

The average total dose of rFVIIa administered was 90.5 μg/kg (± 48.3 μg/kg), with a median dose of 88.1 μg/kg (Fig 1A). The average total dose of FEIBA was 18.6 U/kg (±12.4 U/kg), with a median dose of 14.9 U/kg (Fig 1B). In both groups, the majority of patients received a single dose of either FEIBA or rFVIIa. Both medications were administered either in the operating room after weaning from CPB or during the immediate postoperative period in the CTICU.

There were no statistically significant differences in the overall number or types of clinically significant thromboembolic events between the 2 treatment groups (Table 3). Eight events (13.1%) were observed in the rFVIIa group and 13 (12.1%) in the FEIBA group. The most common thromboembolic complication in the rFVIIa group was cerebral infarction ($n = 4$, 6.6%), and in the FEIBA group, pulmonary embolism ($n = 6$, 5.6%). One patient (0.9%) in the FEIBA group developed an intracardiac thrombus within 24 hours of medication administration. Patients who developed thromboembolic complications did not receive higher doses of either hemostatic agent (Fig 2A and 2B).

The 30-day mortality rates of the rFVII and FEIBA groups were 18% and 10.3%, respectively ($p = 0.15$). The most common cause of death in the rFVIIa group was infection ($n = 4$, 6.6%), and in the FEIBA group, cardiac failure ($n = 4$,