Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery

Howard K. Song, MD, PhD, Frederick A. Tibayan, MD, Ed A. Kahl, MD, Valerie A. Sera, MD, Matthew S. Slater, MD, Thomas G. Deloughery, MD, and Mick M. Scanlan, MD

Objective: Coagulopathy is an important cause of bleeding after complex cardiac surgery. The conventional treatment for coagulopathy is transfusion, which is associated with adverse outcomes. We report our initial experience with the prothrombin complex concentrate FEIBA (factor VIII inhibitor bypassing activity) for the rescue treatment of coagulopathy and life-threatening bleeding after cardiac surgery.

Methods: Twenty-five patients who underwent cardiac surgery with coagulopathy and life-threatening bleeding refractory to conventional treatment received FEIBA as rescue therapy at our institution. This cohort represents approximately 2% of patients undergoing cardiac surgery in our university-based practice during the study.

Results: The patients were at high risk for postoperative coagulopathy with nearly all patients having at least 2 risk factors for this. Aortic root replacement (Bentall or valve-sparing procedure) and heart transplant with or without left ventricular assist device explant were the most common procedures. The mean FEIBA dose was 2154 units. The need for fresh frozen plasma and platelet transfusion decreased significantly after FEIBA administration ($P = .0001$ and $P < .0001$). The mean internationalized normalized ratio decreased from 1.58 to 1.13 ($P < .0001$). Clinical outcomes were excellent. No patient returned to the operating room for reexploration. There was no hospital mortality and all patients were discharged home. One patient who had a central line and transvenous pacemaker developed an upper extremity deep vein thrombosis.

Conclusions: Our initial experience with FEIBA administration for the rescue treatment of postoperative coagulopathy and life-threatening bleeding has been favorable. Further studies are indicated to confirm its efficacy and safety and determine specific clinical indications for its use in patients undergoing cardiac surgery. (J Thorac Cardiovasc Surg 2014;147:1036-40)

Coagulopathy is a frequent complication of cardiac surgery and cardiopulmonary bypass.[1] The causes of coagulopathy are multifactorial, and include excessive fibrinolysis, platelet dysfunction, and coagulation factor deficiency due to consumption and dilution,[1-4] Especially after complex operations, coagulopathy is associated with bleeding and the need for blood component transfusion and surgical reexploration, all of which have been linked to adverse outcomes and prolonged length of stay.[1,2,5-7] The mainstays of treatment for coagulopathy associated with cardiac surgery are antifibrinolytic drug therapy to prevent excessive fibrinolysis, and blood component transfusion to correct platelet and coagulation factor deficiencies. These therapies, however, are frequently ineffective and are themselves associated with adverse outcomes.[7-11] Therefore, there is a need for novel therapies that can effectively and safely treat coagulopathy after cardiac surgery and prevent the complications associated with it.

Several plasma-derived and recombinant coagulation factors are available for systemic administration and have been used for the treatment of coagulopathy after cardiac surgery. Experience with the use of recombinant factor VIIa is increasing and its efficacy is being demonstrated, however this has been associated with thrombotic risk and has a substantial cost.[12-20] Prothrombin complex concentrates (PCCs) are plasma-derived concentrates of vitamin K–dependent factors II, VII, IX, and X.[21-24] There has been some experience with the use of PCCs to reverse warfarin anticoagulation in patients undergoing emergency cardiac surgery but PCCs have not been studied systematically for the treatment of coagulopathy after cardiopulmonary bypass.[25-27] In this study, we report our initial experience with PCCs for the rescue treatment of coagulopathy and life-threatening bleeding after cardiac surgery.

METHODS

Demographic and perioperative clinical information are collected prospectively for all patients undergoing cardiac surgery at Oregon Health

From the Division of Cardiothoracic Surgery, Department of Anesthesiology and Perioperative Medicine, Division of Hematology and Medical Oncology, Oregon Health & Science University, Portland, Ore.

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Address for reprints: Howard K. Song, MD, PhD, Division of Cardiothoracic Surgery, Mail Code L353, OHSU, 3181 SW Sam Jackson Park Rd, Portland, OR 97239 (E-mail: songh@ohsu.edu).

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Abbreviations and Acronyms
FEIBA = factor VIII inhibitor bypassing activity
LVAD = left ventricular assist device
PCC = prothrombin complex concentrates

& Science University Hospital. An institutional pharmacy database was surveyed to identify all patients who underwent cardiac surgery and received the PCC product factor VIII inhibitor bypass activity (FEIBA; Baxter Healthcare Corporation; Deerfield, Ill) from July 2011 to October 2012.[21] Twenty-five patients were identified and included in this study.

Intraoperative ε-aminocaproic acid was administered to all patients as a 5-g intravenous loading dose and 30 mg/kg/h infusion. An additional 5 g was included in the cardiopulmonary bypass machine prime. All patients underwent standard heparinization (300-400 IU/kg) before cardiopulmonary bypass and activated clotting times were maintained at greater than 480 seconds. At the conclusion of cardiopulmonary bypass, heparin was reversed with protamine sulfate at a dose based on the measured level of circulating heparin. A cell saver and cardiotomy suction were used in all cases.

Patients who were treated with therapeutic levels of warfarin at the time of surgery received fresh frozen plasma (4-6 units) before weaning from bypass. After heparin reversal, any observed coagulopathy was treated empirically with standard transfusion of platelets, fresh frozen plasma, and cryoprecipitate. Transfusion was also guided by point-of-care thromboelastography, prothrombin and activated partial thromboplastin times, and platelet count. Packed red blood cells were transfused to maintain a hematocrit greater than 21%. If the surgeon noted that coagulopathy and life-threatening bleeding persisted despite conventional treatment, FEIBA was administered (1000-4000 units) as a slow intravenous push. FEIBA was only administered intraoperatively before chest closure.

Nominal data are presented as frequencies and percentages. Continuous data are reported with the mean, range, and standard deviation. Comparisons before and after administration of FEIBA (fresh frozen plasma and platelet transfusion, internationalized normalized ratio, partial thromboplastin time, and fibrinogen) were performed with the two-tailed Student *t* test.

Institutional review board approval was obtained for this study. The requirement for individual consent was waived.

RESULTS

Twenty-five patients who received FEIBA as rescue therapy after failing conventional treatment of coagulopathy were identified. This represents approximately 2% of all patients undergoing cardiac surgery at our institution during the study period. Demographic and clinical data are summarized in Table 1. The mean age of the patients was relatively low for an adult cardiac surgery population (49.6 years) and reflects the types of surgical procedures performed. All patients had either an aortic procedure, a left ventricular assist device (LVAD) implant, or a heart transplant with or without an LVAD explant. There were no coronary artery bypass procedures performed in this group. The preoperative hematologic profile of most patients was unremarkable, with the exception of the international normalized ratio. Twelve patients were anticoagulated with warfarin at the time of their surgery. In all instances, these patients had heart failure and required anticoagulation because of ongoing LVAD support or were anticoagulated because of their risk or previous history of left ventricular thrombus. The urgent or emergency nature of their procedures did not allow time for warfarin to be stopped before their surgery. Patients with an LVAD admitted for heart transplantation did receive a dose of intravenous vitamin K in the hours before their heart transplant as part of our institutional protocol.

All patients had at least 1 risk factor for the development of coagulopathy after cardiac surgery, and most had multiple risk factors (Table 2). Most risk factors were related to the patient's clinical condition or planned procedure and were apparent before the operation. The most common risk factors for coagulopathy were prolonged cardiopulmonary bypass time, preoperative anticoagulation, aortic surgery, and redo sternotomy.

All patients had complete reversal of heparinization with protamine after cessation of cardiopulmonary bypass. Sufficient protamine was administered so that circulating heparin levels were undetectable and activated clotting times were returned to baseline levels. Coagulopathy was then treated with conventional blood product transfusion. Blood product transfusion was typically empiric with additional guidance from point-of-care thromboelastography, platelet counts, and prothrombin times. If the surgeon noted that a patient had ongoing coagulopathic bleeding despite these measures and no clear surgical source could be identified, FEIBA was administered as a rescue treatment. The mean FEIBA dose was 2154 units (Table 3). Early in our experience, we gave FEIBA in 1000-unit increments to achieve the desired hemostatic effect. Later, we simply administered 2000 units in a single dose, which was typically sufficient. Eighteen patients received 2000 units.

Blood product use decreased substantially after FEIBA administration (Table 3). Patients received a mean fresh frozen plasma transfusion of 4.76 units before FEIBA and 0.68 units after FEIBA ($P = .0001$). Platelet transfusion was reduced from 2.76 units to 0.52 units after FEIBA administration ($P < .0001$). Seventeen patients received no further plasma or platelet transfusion in the postoperative period after FEIBA administration. Cryoprecipitate was only given to 2 patients in the series. The mean packed red blood cell transfusion for patients in the perioperative period was 1.16 units and 16 patients did not receive red blood cell transfusion. No recombinant coagulation factors such as factor VIIa were given to any patients in the series.

Pre- and post-FEIBA dosing coagulation studies were available for comparison in 17 patients (Table 4). The international normalized ratio was significantly reduced in these patients without a notable change in partial thromboplastin time or fibrinogen levels. Blood loss was not measured intraoperatively. In the first 3 postoperative days, the mean chest tube drainage was 664, 549, and

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