Recombinant Factor VIIa to Control Excessive Bleeding Following Surgery for Congenital Heart Disease in Pediatric Patients

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The purpose of this article is to evaluate the efficacy of recombinant factor VII (rFVIIa) in the treatment of bleeding following cardiac surgery in a pediatric population. The study included a case series of postcardiac surgical patients with chest tube output of ≥ 4 mL/kg/h for the initial 3 postoperative hours who received rFVIIa. Chest tube output for the 3 hours before and the 3 hours after rFVIIa was compared using a paired *t* test. In addition, chest tube output for the initial 3 postoperative hours and the 3 hours following rFVIIa was compared to 8 control patients who did not require rFVIIa. Recombinant factor VIIa was administered to 9 children (age = 9 ± 4 years) following repair of tetralogy of Fallot (6), closure of ventricular septal defect (1), closure of sinus venosus atrial septal defect (1), and mitral valve repair (1). Chest tube output for the initial 3 postoperative hours prior to the administration of rFVIIa was 5.8 ± 2.8 mL/kg/h and decreased to 2.0 ± 1.3 mL/kg/h for the 3 hours following the administration of rFVIIa (*P* = .002). In the patients that did not receive rFVIIa, chest tube output for the first 3 postoperative hours was 1.6 ± 0.9 mL/kg/h and 1.2 ± 0.6 mL/kg/h for the next 3 hours (*P* = nonsignificant when compared to chest tube output for the 3 hours following rFVIIa in patients who received rFVIIa). No adverse effects were noted. Recombinant factor VIIa decreased chest tubing bleeding following cardiac surgery in children. Given its potential therapeutic impact, rFVIIa warrants further investigation in the pediatric cardiac population.

Key words: *recombinant factor VIIa, chest tubing bleeding, congenital heart disease, pediatric cardiac patients*

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Various etiologic factors may be responsible for coagulation disturbances following cardiopulmonary bypass (CPB) and surgery for congenital heart disease, including qualitative or quantitative platelet disorders, disseminated intravascular coagulation, dilution of coagulation factors due to the pump prime, fibrinolysis, and residual heparin effect. Postoperative coagulation dysfunction may be particularly common in patients with cyanotic congenital heart disease [1]. When clinically significant bleeding occurs, therapy includes correction of coagulation function with the administration of blood products including cryoprecipitate, fresh frozen plasma (FFP), and platelet concentrates according to laboratory evaluation of the coagulation profile. Despite its efficacy, problems exist with the use of FFP including the potential for the transmission of infectious diseases, volume overload, anaphylactoid reactions, alterations in serum ionized calcium, and decreases in mean arterial pressure [2]. In addition, the time for thawing and administration may require 30 to 60 minutes depending on the patient's cardiorespiratory status and ability to tolerate rapid fluid administration.

Various coagulation factors including factor VII can now be synthesized using recombinant DNA technology. In 1988, the first patient was treated with recombinant factor VIIa (rFVIIa) [3]. To date, the majority of experience with rFVIIa has been in the treatment of patients with hemophilia who

have developed autoantibodies against factor VIII, making infusions of factor VIII ineffective during bleeding episodes [4]. Following its efficacy in the hemophilia population, there is an increasing body of clinical experience with rFVIIa in other scenarios in pediatric-aged patients [5-9]. To date, the reported experience with rFVIIa following cardiothoracic surgical procedures has been anecdotal with its use in only 2 pediatric-aged patients [10,11]. We present our experience with the use of rFVIIa to treat excessive blood loss following CPB and cardiac surgery in pediatric patients.

Methods

Review of these data for this case series was approved by the institutional review board of the University of Missouri. The patients reported herein were operated on during the January 2003 trip of Heart Care International to Santo Domingo, Dominican Republic. Heart Care International is a nonprofit organization that helps organize and train medical personnel in countries outside of the United States with a need for pediatric cardiology and cardiac surgery services. As the Dominican Republic is a developing country, there are limitations regarding the availability and safety of blood products, including FFP. There is also no availability for the rapid determination of coagulation profiles.

Chest tube output for the first 3 postoperative hours was evaluated, and patients who had a mean blood loss of ≥ 4 mL/kg/h for 3 consecutive hours (≥ 12 mL/kg for the first 3 postoperative hours) were administered rFVIIa as a single bolus dose of 90 μg/kg. For comparison, the amount of chest tube output was evaluated in 8 patients with blood loss of less than 4 mL/kg/h for the first 3 postoperative hours. These patients did not receive rFVIIa. These patients were selected since they matched the rFVIIa patients in regard to age, weight, surgical procedure, CPB time, and aortic cross-clamp time.

Following the dose of rFVIIa, chest tube output was evaluated for the next 3 hours. Demographic data included age, weight, gender, and underlying congenital cardiac defect. Data regarding the surgical procedure included CPB time and aortic cross-clamp time. Chest tube output before and after rFVIIa was compared using a paired, 2-tailed *t* test. A nonpaired, 2-tailed *t* test was used to compare demographic data (age, weight), CPB time, aortic cross-clamp time, and chest tube output between the 2 groups. All data are presented as the mean ± standard deviation, with $P < .05$ considered significant.

Results

Nine patients received rFVIIa during the 2003 surgical trip. There were 8 patients that served as the comparison group (Table 1). There was no difference between the groups with regard to age, weight, CPB, and aortic cross-clamp time (Table 1). The surgical procedures are listed in Table 1. Chest tube output for the initial 3 postoperative hours before the administration of rFVIIa was 5.8 ± 2.8 mL/kg/h and decreased to 2.0 ± 1.3 mL/kg/h for the 3 hours following the administration of rFVIIa. In the patients that did not receive rFVIIa, chest tube output for the first 3 postoperative hours was 1.6 ± 0.9 mL/kg/h and 1.2 ± 0.6 mL/kg/h for the next 3 hours (Table 1). No patient required mediastinal reexploration to control postoperative bleeding. No repeated doses of rFVIIa were administered for ongoing or recurrence of chest tube bleeding. No adverse effects (hemodynamic changes, thromboembolic complications) were noted related to the administration of rFVIIa.

Discussion

In many of the previous reports describing the administration of rFVIIa to infants and children, rFVIIa has been administered for life-threatening bleeding when conventional blood product therapy (FFP, cryoprecipitate, platelet concentrates) failed or time precluded their use. To date, the majority of these reports have been anecdotal without a means of measuring blood loss before and after the administration of rFVIIa. In the current cohort of patients, there was an objective measure (chest tube output) that demonstrated a significant decrease following the administration of rFVIIa. The output following rFVIIa matched that of the control group, in whom bleeding was not a problem. Given the ethical problems regarding the withholding of therapy in the bleeding patient, there was no placebo-control group (bleeding patients who did not receive rFVIIa) but rather a nonbleeding cohort to provide what might be considered normal values for chest tube output.

The patients who received rFVIIa all had excessive chest tube output (≥ 4 mL/kg/h) that decreased to a mean of 2 mL/kg/h following the

Table 1. Data of Recombinant Factor VII (rFVIIa) and Control Patients

	rFVIIa Patients	Control Patients
Number of patients	9	8
Age, y	9 ± 4	10 ± 3
Weight, kg	29 ± 12	28 ± 11
Surgical procedure (repair of)		
Tetralogy of Fallot	6	5
Ventricular septal defect	1	0
Mitral valve repair	1	0
Sinus venosus atrial septal defect	1	0
Primum atrial septal defect	0	3
Cardiopulmonary bypass time, min	97 ± 55	113 ± 37
Aortic cross-clamp time, min	68 ± 26	68 ± 23
First 3-hour chest tube output, mL/kg/h	5.8 ± 2.8	1.6 ± 0.9*
Next 3-hour chest tube output, mL/kg/h	2.0 ± 1.3**	1.2 ± 0.6[a]

*P = .002 compared to first 3 hours of chest tube output of rFVIIa patients.
**P = .0011 compared to first 3 hours of chest tube output prior to rFVIIa.
a. Nonsignificant compared to chest tube output after rFVIIa.

administration of rFVIIa. This value of 2 mL/kg/h was similar to the nonbleeding, control patients.

To date, there are only 2 reports of the use of rFVIIa in the pediatric cardiac population. Al Douri et al reported the successful use of rFVIIa in a case series of 5 patients with bleeding and coagulation dysfunction following cardiac surgery [10]. One of these was a 2.5-year-old child with an intraoperative blood loss of 4.5 L during repair of an atrial septal defect and an arterial switch procedure for transposition of the great vessels. The bleeding, which continued despite the administration of FFP and platelets, ceased after a single dose of rFVIIa (30 μg/kg). Tobias et al noted similar efficacy using rFVIIa to control bleeding following cardiac surgery and CPB in a 4-month-old, 3.7-kg infant with postoperative pulmonary hypertension [11]. Chest tube output averaged approximately 10 mL/kg/h for the first 3 postoperative hours, and laboratory evaluation revealed a prothrombin time (PT) of 36.6 seconds (normal PT = 11.5-13.2 seconds), international normalized ratio (INR) of 6.8 (normal INR = 0.8-1.4), and partial thromboplastin time of 96.5 seconds (normal = 22.9-31.7 seconds) with a platelet count of 80,000/mm^3. Following rFVIIa, the chest tube output was 3 mL/kg/h for the subsequent 3 hours, and there were no additional bleeding concerns. Similar anecdotal efficacy in the control of postoperative bleeding has been reported in adult patients following cardiac surgery [12-16]. This experience included 1 patient following coronary artery bypass grafting [12]; 3 patients following mitral valve surgery, 2 of whom were Jehovah's witnesses [13,14]; and 2 patients with left ventricular assist devices in place [15,16].

With any bleeding scenario, attempts should be made to exclude surgical causes of bleeding and reverse, when possible, the etiologic factors contributing to the coagulopathy (hypoperfusion, acidosis, hypothermia, etc), along with blood product therapy for abnormal coagulation function. In usual clinical practice, we would suggest an evaluation of coagulation function with therapy directed by the results. This may include protamine for residual heparin effect, FFP and/or cryoprecipitate for dilutional coagulopathy, or platelet concentrations for thrombocytopenia. When these therapies fail or are unavailable (religious objections, time constraints), our current report and previous anecdotal experience from the literature suggest that rFVIIa may be effective. Recombinant FVIIa can be quickly reconstituted from powder with a small volume of saline (2-3 mL for the 1.2-mg vial) and can be administered intravenously over 2 to 3 minutes. In addition to its effects on coagulation function, augmentation of platelet function has been demonstrated, thereby suggesting a secondary effect in patients with quantitative or qualitative platelet disorders [17,18].

Although clinical experience is somewhat limited, no significant adverse effects have been noted in the pediatric population. As rFVIIa requires tissue factor for activation and tissue factor is released only at the site of endothelial injury, the risk of excessive thrombogenesis should be limited. However, there are no data regarding its use in patients with systemic-to-pulmonary shunts who may be at risk for thrombotic complications. The current cohort did not include this subset of patients.

Dosing recommendations in the pediatric-aged patient are extrapolated from the adult literature supplemented by information from the pediatric hemophiliac population. Doses ranging from 40 to 100 μg/kg have been reported in the nonhemophiliac population [5-9]. Our current practice includes an initial bolus dose of 90 μg/kg repeated in 2 hours if needed. This dosing regimen would result in an average cost of approximately $1000 (cost for a 1.2-mg vial) for a 10-kg patient.

Given its potential therapeutic impact, rFVIIa warrants further investigation in the pediatric cardiac population. An obvious weakness of our cur-

rent report is the lack of a true control group. Given the previously mentioned issues with the use of FFP in the current setting, we did not feel a comparison with FFP was appropriate. However, in a more controlled setting, this type of comparison is needed. We would doubt that a placebo-controlled trial is feasible in any setting since there is a need to ensure effective therapy of coagulation disturbances in this clinical scenario.

Despite its potential benefits, cost remains a consideration. Recombinant FVIIa is approximately $0.85 per microgram. This information must be factored in when considering the cost of the agent itself versus potential benefits of decreased use of blood products, decreased intensive care unit stays, or potentially decreased patient morbidity and mortality. However, with excessive bleeding, it is feasible that the need for blood products (FFP and/or packed red blood cells) in addition to repeated laboratory testing could be greater than the cost of rFVIIa. As recent studies have demonstrated potential morbidity associated with allogeneic blood products, including an increased risk of nosocomial infections with prolongation of hospital stays [19,20], it is feasible that these hidden costs associated with allogeneic blood products may further shift the cost-benefit ratio in the favor of rFVIIa. However, until such studies are completed, in the absence of contraindications to the use of FFP, rFVIIa should be considered as rescue therapy.

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