Recombinant Factor Seven Therapy for Postoperative Bleeding in Neonatal and Pediatric Cardiac Surgery

Hemant S. Agarwal, MBBS, Jo E. Bennett, BS, Kevin B. Churchwell, FAAP, MD, Karla G. Christian, MD, Davis C. Drinkwater Jr, MD, Yi He, MS, and Mary B. Taylor, MD

Department of Pediatrics, Division of Pediatric Critical Care, Department of Pediatric Cardiothoracic Surgery, and Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee

Background. **Severe bleeding is a major complication in the postoperative pediatric cardiac surgery patients. We evaluated the efficacy and safety of recombinant factor seven (rFVIIa) therapy in this patient population.**

Methods. **A retrospective unmatched case-control study for the previous five years in a single institution was undertaken. Patients with severe bleeding treated with rFVIIa therapy (study group) were compared with patients treated with blood products only (control group) using analysis of variance. Mediastinal bleeding, blood products transfusion, and coagulation studies before and six hours after the first dose of rFVIIa therapy were analyzed using the Student paired *t* test. The dose, frequency, and side-effects of rFVIIa therapy were studied.**

Results. **Forty-six patients with severe bleeding were studied. Twenty-three of 24 patients in the study group, including 12 patients placed on extracorporeal membrane oxygenation (ECMO), responded to rFVIIa therapy (mean dose 43 ± 22.9 μg/kg/dose). There was significant reduction in chest tube drainage (from 52.3 ± 36.1 mL/kg/hour to 18.8 ± 20.9 mL/kg/hour, $p = 0.0003$) along with significant reduction of blood products transfusion ($p < 0.001$) in the study group patients as compared with control group patients. One patient who failed to respond had surgical bleeding. Two patients developed major thrombotic complications that included clots in the ECMO circuit and thrombosis at bleeding arterial line site resulting in limb ischemia. Four additional patients in the study group developed mediastinal clots. Overall, 25% of patients developed thrombosis after rFVIIa therapy.**

Conclusions. **The rFVIIa therapy seems to be an effective treatment for severe bleeding in postoperative pediatric cardiac surgery patients in the absence of surgical bleeding. It must be judiciously used in patients bleeding from multiple sites or having preexistent clots in the ECMO circuit to prevent major thrombotic complications.**

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Postoperative bleeding is a major complication in neonates and infants undergoing cardiac surgery. Mediastinal blood loss as high as 15 to 110 mL/kg has been reported in some reviews [1]. Limited therapeutic options are available to treat severe bleeding. Blood products, including fresh frozen plasma, cryoprecipitate, and pooled platelets, are administered to correct the coagulopathy and packed red blood cells are concurrently given to correct the anemia. Administration of large amounts of blood product transfusion has the risk of transfusion-related reactions and disease transmission. Alternative therapies like antifibrinolytic drugs, including tranexamic acid, aprotinin, and epsilon-aminocaproic acid, are more effective prophylactically than for treatment of postoperative bleeding [2]. Reexploration of the chest in patients with severe bleeding reveals a surgically manageable source of bleeding in less than 50% of cases [3]. Thus, an effective and safe medical therapy needs to be studied for these patients.

Recombinant factor VIIa (rFVIIa, Novoseven; Novo Nordisk, Princeton, NJ) was introduced in the 1980s to treat bleeding in hemophilia patients [4]. It is currently being used as an off-label drug for treatment of severe bleeding in clinical conditions such as trauma, adult cardiac surgery, and liver transplantation [5–7]. Case reports and limited case series favor the role of rFVIIa therapy in postoperative pediatric cardiac surgery patients [8–12] although a large study is still lacking. We reviewed our five years experience of rFVIIa therapy for severe postoperative bleeding, including patients placed on extracorporeal membrane oxygenation (ECMO) to study the efficacy and safety of rFVIIa.

Material and Methods

This retrospective study was conducted in the pediatric cardiac intensive care unit (PCICU) of the Monroe Carell Jr. Children's Hospital at Vanderbilt. An approval from

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Address correspondence to Dr Taylor, Vanderbilt Children's Hospital, 2200 Children's Way, 5121 B Doctors' Office Tower, Nashville, TN 37232-9075; e-mail: mary.b.taylor@vanderbilt.edu.

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Table 1. Preoperative and Immediate Postoperative Details of Patients

Characteristics	Study Group (n = 24)	Control Group (n = 22)
Demographic details:		
Age (days)	9.5[a] (4–3,285)	7[a] (2–240)
Weight (kgs)	3.5[a] (2.4–51)	3.2[a] (2–6.7)
Cardiac defect:		
HLHS	12	8
TGA	6	6
AS	2	2
BDG	1	2
OTHERS	3	5
ECMO	12	15

[a] Median; range in parentheses.

AS = aortic stenosis; BDG = bidirectional Glenn shunt; ECMO = extracorporeal membrane oxygenation; HLHS = hypoplastic left heart syndrome; TGA = transposition of great arteries.

the Institutional Review Board was obtained including waiver of consent authorization. Medical charts of all patients who had severe bleeding in the immediate postoperative period after cardiac surgery from January 2000 to December 2004 were reviewed. Children less than 19 years of age who had no known bleeding disorder were included in the study. Patients who received rFVIIa in the immediate postoperative period for severe bleeding were categorized to a study group and patients who were managed with blood products only to control their bleeding were categorized to the control group. Demographic characteristics such as age, weight, sex, and preoperative cardiac defect were noted. Operative records were reviewed for cardiopulmonary bypass (CPB) time, aortic cross-clamp time, and the surgical procedures performed. Patients placed on ECMO postoperatively for cardiopulmonary support were also included in the study. Any patient in the control group who responded to surgical exploration for severe bleeding was excluded from the control group.

For this retrospective review, selection of patients with severe bleeding was defined in each patient based on mediastinal chest tube blood loss. At the completion of surgery after being weaned off the CPB, all patients were monitored on an hourly basis for chest tube bleeding. Mediastinal bleeding, more than 10 mL/kg per hour in neonates and infants or more than 100 mL/hour in adolescents for at least one hour time period, was used to identify patients for inclusion in the study group. Hematology laboratory tests including prothrombin time (PT), activated partial thromboplastin time (PTT), international normalized ratio (INR), platelet count, fibrinogen levels, and hematocrit were evaluated. Bleeding and anemia were empirically controlled by the attending physician by administration of blood products that generally included the following: platelets, 1 unit/10 kg; fresh frozen plasma, 10 to 15 mL/kg; cryoprecipitate, 1 unit/5 kg; and packed red cells, 10 to 15 mL/kg. Further blood products administration was based on laboratory results of INR, PT, PTT, fibrinogen levels, platelet count, and hematocrit values. Surgical reexploration was constantly assessed by the attending physician in consultation with the surgeon. Administration of rFVIIa at this time period was based on the discretion of the attending physician. Because rFVIIa was employed as rescue therapy for critically ill patients and there were no experimental interventions, informed consent was deemed unnecessary. Once decision was made to give rFVIIa, a bolus injection was administered and the dose given was at the discretion of the attending physician. Mediastinal chest tube drainage and the requirement of blood products administration was reassessed after rFVIIa therapy. Patients did not receive any further rFVIIa if there was significant reduction in the chest tube drainage that was sustained over the next two to four hours. However, if the chest tube drainage did not show a sustained downward trend over the next few hours, coagulation studies and hematocrit values were repeated and blood products were administered. Further administrations of rFVIIa doses and (or) mediastinal reexploration were at the discretion of the attending physician and the surgeon.

The safety of the drug was monitored in all the patients who received rFVIIa therapy. Complications known after rFVIIa therapy, especially thrombosis of blood vessels in the patient or thrombosis in the ECMO circuit, were specifically assessed. Thrombosis of the ECMO circuit was assessed by visual inspection and changes in the pressure gradients in the ECMO circuit tubing. Thrombosis of blood vessels in the patients were assessed by clinical examination of the peripheral pulses, bedside portable Doppler testing of the pulses, and distal tissue perfusion. Mediastinal clots were assessed by lack of chest tube drainage associated with distention of the mediastinum in the delayed sternal closure patients.

Mediastinal chest tube bleeding and volume of blood products administered, including fresh frozen plasma, cryoprecipitate, platelets, and packed red cells given to the patient, and laboratory hematology results were analyzed in all patients using the statistical software SAS (SAS Institute Inc, Cary, NC). All continuous results are expressed as mean ± standard deviation. Analysis of variance (ANOVA) was used to compare data in the study group patients before, and for six hours after,

Table 2. Recombinant Factor Seven (rFVIIa) Therapy Administered to the Study Group Patients

Number of rFVIIa Doses	Amount of rFVIIa Dose (μg/kg)	Dose Interval (hours)	Response to rFVIIa
1 (n = 15)	46.9 ± 29.3	OR to 1st dose: 3.9 ± 1.7	Yes
2 (n = 7)	46.8 ± 16.3	1st to 2nd dose: 3.3 ± 2.9	Yes
3 (n = 1)	31.6	2nd to 3rd dose: 2	Yes
4 (n = 1)	24.3 ± 6.9	3rd to 4th dose: 2	No

n = number of patients; OR = operating room.