Thrombotic Risk of Recombinant Factor Seven in Pediatric Cardiac Surgery: A Single Institution Experience

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Background. **Recombinant activated factor seven (rFVIIa) is increasingly being used as a hemostatic adjunct in pediatric cardiac surgery. We evaluated the thrombotic safety profile of rFVIIa in pediatric congenital heart disease (CHD) surgery.**

Methods. **This was a retrospective matched case-control study over six years at a single institution. Patients who received rFVIIa after CHD surgery were matched to controls based on age, diagnosis, and procedure. We compared thrombosis, hemorrhage, transfusions, length of stay, and repeat procedures between groups.**

Results. **Twenty-five patients received rFVIIa (mean dose: 70 mcg/kg); 50 controls were matched. There was no significant difference in the rate of thrombosis between patients who received rFVIIa and controls (8% vs 4%). After rFVIIa, there was a significant reduction in transfusion volume (median 77.1 mL/kg vs 14.6 mL/kg; $p < 0.001$) as well as a significant decrease in hemorrhagic chest tube output (8.3 ± 1.6 mL/kg/hour vs 1.4 ± 0.3 mL/kg/hour; mean ± standard error of the mean; $p < 0.001$). No difference was seen in intensive care unit or hospital length of stay or mortality between patients receiving rFVIIa and controls.**

Conclusions. **The rFVIIa therapy did not increase thrombotic complications when used as rescue therapy after CHD surgery but did appear to decrease bleeding complications in this small cohort.**

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Severe postoperative bleeding is a major source of morbidity and mortality in pediatric patients undergoing cardiac surgery and cardiopulmonary bypass for correction of congenital heart defects (CHD). Blood loss and blood product transfusion can exceed 100 mL/kg, and bleeding requiring surgical reexploration occurs in 1% of all pediatric cardiac surgery patients [1]. Many times there is no identifiable source of bleeding, and the bleeding may be prolonged despite standard therapy with blood products. In addition to problems directly related to blood loss such as need for surgery, hypovolemic shock, and decreased oxygen delivery, these patients are also at increased risk for infectious complications due to the potential exposure to large numbers of blood products as well as other complications such as transfusion-related acute lung injury [2–4].

In addition to increased risk of bleeding, patients with CHD are also at increased risk of thrombotic complications. This is especially common in patients with single-ventricle physiology both prior to and after Fontan repair, with the reported incidence of thromboembolic events ranging from 3% to 20% [5, 6]. This thrombosis risk may be due to a variety of factors, including protein-losing enteropathy, endothelial dysfunction, and abnormalities in clotting factors even without protein loss [6, 7]. These abnormalities appear most pronounced in the first 1 to 2 days after surgery and are not unique to single-ventricle physiology [8, 9].

Recombinant activated factor VII, or rFVIIa (NovoSeven; Novo Nordisk, Princeton, NJ), is a prohemostatic agent approved by the Food and Drug Administration in 1999 to treat bleeding in patients with hemophilia and inhibitors to factor VIII or IX; it has subsequently gained additional approval for the treatment of factor VII deficiency. Since its introduction, rFVIIa has been widely used as an off-label hemostatic adjuvant therapy. In several case series, some with cardiac surgery patients, it has been reported to reduce blood transfusions, chest tube output, and other bleeding complications [1, 10–15]. To date there have been few randomized controlled studies looking at rFVIIa use in off-label indications [14, 16–18]. Despite its increasing use, there have been few

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Abbreviations and Acronyms

aPTT = Activated partial thromboplastin time
AS/AI = Aortic stenosis and (or) insufficiency
CHD = Congenital heart disease
DIC = Disseminated intravascular coagulation
DKS = Damus-Kaye-Stansel
d-TGA = d-transposition of the great arteries
DVT = Deep venous thrombosis
FFP = Fresh frozen plasma
HIT = Heparin-induced thrombocytopenia
HLHS = Hypoplastic left heart syndrome
IVC = Inferior vena cava
LV = Left ventricle
NCH = Nationwide Children's Hospital
PA = Pulmonary artery
PRBC = Packed red blood cells
PT = Prothrombin Time
rFVIIa = Recombinant activated factor seven
RV = Right ventricle
TAPVR = Total anomalous pulmonary venous return

studies of any kind in the setting of pediatric congenital heart surgery, and controversy remains regarding both its safety and effectiveness in this population [19, 20]. Given the potential increased risk for thrombosis found in CHD patients, there is concern that the routine use of rFVIIa in pediatric patients undergoing cardiac surgery will result in an unacceptably high rate of thrombotic events. In recent studies, there is disagreement as to whether there is an increased rate of thrombotic complications in pediatric CHD patients who receive rFVIIa postoperatively, although these studies were designed primarily to examine the efficacy of rFVIIa [19, 20]. In light of these controversies, the primary objective of this study was to examine the thrombotic safety profile of rFVIIa administered to CHD surgery patients at our institution. To do so, we retrospectively assessed the incidence of clinically significant thrombosis in patients who did or did not receive rFVIIa who were matched for well-recognized risk factors for CHD-associated thrombosis (age, CHD diagnosis, and type of repair) [6, 8, 21]. Secondary outcomes included assessments of mortality, nonthrombotic morbidity, length of stay, and efficacy.

Patients and Methods

The study protocol was approved by the Institutional Review Board of the Nationwide Children's Hospital (NCH), Columbus, Ohio (IRB05-00503). Written informed consent was waived due to the retrospective study design.

Patients

Patients who received rFVIIa were identified from a hospital pharmacy database. All patients who received rFVIIa either intraoperatively or within 1 week after surgery for congenital heart disease during the period from January 1, 1999 to December 31, 2005 were considered for inclusion. Patients were excluded if they had a diagnosis of hemophilia, a diagnosis of congenital factor VII deficiency, were greater than 21 years old, or had previously received rFVIIa. Controls from the same time period were selected and matched for age, diagnosis, and type of procedure in order to control for known epidemiologic determinants of thrombotic risk in CHD. To be considered a match for age, a control needed to be within 1 month if less than 1 year old, within 6 months if between 1 year and 5 years old, within 1 year if between 5 years and 10 years old, and within 2 years if greater than 10 years old. If no age-matched controls were found, then 2 or 3 of the closest age matches were selected. This only occurred with patients less than 1 year old, and in all cases the age was within 3 months.

Standard Institutional Cardiopulmonary Bypass Regimen

During the study time frame, saline-primed bypass circuits were preferred for patients greater than 5 kg and were primed with blood for children less than 5 kg. Some Jehovah's Witness patients weighing less than 5 kg were saline primed. Although the records were incomplete, we estimate that about 50% of both cases and controls were blood primed. Blood transfused in the primed circuit or during cardiopulmonary bypass was not included in the transfusion requirement analysis. Bypass was performed using the Jostra HL20 (Maquet Cardiopulmonary AG, Hirrlingen, Germany) with either the Terumo Capiox SX10R or SX18R oxygenators for children or the Terumo Baby Rx for infants (Terumo Cardiovascular Systems, Ann Arbor, MI). The patients were heparinized during bypass using reversal with protamine sulfate at the end of the case. The patients also received aprotinin during bypass: loading dose 10,000 KIU/kg; pump dose 10,000 KIU/kg; and maintenance dose 10,000 KIU/kg/hour. Aprotinin was discontinued at the end of the case and not typically given in the postoperative setting.

Standard Institutional rFVIIa Usage

In our institution, rFVIIa is typically used as rescue therapy for bleeding observed in the operating room (OR) or the intensive care unit (ICU) that is refractory to standard therapy with blood products. The typical transfusion practice for management of bleeding without an identifiable surgical source is as follows. A total of 5 to 10 mL/kg of apheresis platelets and 10 mL/kg of fresh frozen plasma are empirically given for excessive bleeding risking hemodynamic compromise. If there is hemodynamic instability or laboratory evidence of anemia, then 15 to 20 mL/kg of packed red blood cells are also transfused. Cryoprecipitate (1 unit/10 kg) may be given based on abnormal fibrinogen levels. If bleeding persists despite normal temperature, pH, and calcium, these transfusions are typically repeated. If laboratory values such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, or platelet count are available, specific blood products may be chosen based on these