FULL LENGTH ARTICLE

Single center experience on dosing and adverse events of recombinant factor seven use for bleeding after congenital heart surgery

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There are limited data on the relationship between the administered dose of recombinant factor seven (rFVIIa) and the development of adverse clinical outcomes after congenital heart surgery. This single institution case series reports on dosing, adverse events, and blood product usage after the administration of rFVIIa in the congenital heart surgery patient population. A retrospective review identified 16 consecutive pediatric patients at an academic, free-standing, children's hospital who received rFVIIa to curtail bleeding following congenital heart surgery between April 2004 and June 2012. Patients were assessed for survival to hospital discharge versus in-hospital mortality and the presence or absence of a major neurological event during inpatient hospitalization. The median age at surgery was 6.8 months (range: 3 days–42 years). Seven patients (44%) survived to hospital discharge and nine patients (56%) died. The cause of mortality included major neurological events (44%), uncontrolled bleeding (33%), and sepsis (23%). Eight patients (50%) required extracorporeal membrane oxygenation support following congenital heart surgery. The median cumulative rFVIIa dose administered was 97 mcg/kg, and the median cumulative amount of blood products administered was 452 ml/kg. In conclusion, this case series underscores the need to prospectively evaluate the effect that rFVIIa has on patient survival and the incidence of adverse events, including thrombotic and major neurological events, in congenital heart surgery patients. Ideally, a randomized, multicenter study would provide the sufficient numbers of patients and events to test these relationships.

Keywords: Congenital heart disease, Recombinant factor VIIa, Cardiac surgery, ECMO, Bleeding

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Introduction

The repair of complex congenital heart defects in children and adults using cardiopulmonary bypass (CPB) can be associated with a high risk of severe coagulopathy and hemorrhage [1]. The multifactorial causes of these morbidities include hemodilution, systemic inflammatory response, and immature coagulation/platelet systems in neonates [2]. Limited therapeutic options are available to treat severe bleeding once a surgically correctable etiology has been ruled out.

Recombinant factor seven (rFVIIa, NovoSeven RT; Novo Nordisk, Princeton, NJ) was introduced in the 1980s to treat or prevent bleeding in patients with hemophilia or factor VII deficiency [3]. Although labeled to be used for its hemostatic effects directly at the site of endothelial injury, rFVIIa has been utilized off-label as a general hemostatic agent in patients with intractable hemorrhage following congenital heart surgery (CHS) [4]. It has also been used as an off-label drug for bleeding following trauma, surgery, and extracorporeal membrane oxygenation (ECMO) support.

Activated factor VIIa initiates hemostasis by the formation of a complex with tissue factor (TF), a transmembrane protein that is released as a result of blood vessel or tissue injury. The TF-FVIIa complex activates factor X, which then induces thrombin formation from pro-thrombin. Thrombin generation is amplified by the interaction of platelets and factors V, VII, and IX with factor Xa. Thrombin is crucial for the formation of a stable fibrin plug that is resistant to premature fibrinolysis. In addition, rFVIIa promotes platelet function independent of TF activation [5].

Intervention with a potent pro-coagulant compound such as rFVIIa has the potential to restore hemostasis in patients with intractable hemorrhage [6,7]. It also has the potential to cause limb ischemia, as well as significant pathologic thrombosis and related major neurological events (MNE) leading to death [8]. This report serves as a single center case series to evaluate cumulative rFVIIa doses, transfusion requirements, and outcomes following use in CHS patients.

Abbreviations

rFVIIa	recombinant factor seven
CPB	cardiopulmonary bypass
CHS	congenital heart surgery
ECMO	extracorporeal membrane oxygenation
TF	tissue factor
MNE	major neurological events
RACHS	risk adjustment for congenital heart surgery
FFP	fresh frozen plasma
PRBC	packed red blood cells
ACT	activated clotting time
IHM	in-hospital mortality
CPBT	cardiopulmonary bypass time
CCT	cross clamp time
CAT	circulatory arrest time
PT	prothrombin time
PTT	partial thromboplastin time
INR	international normalized ratio

Patients and methods

We reviewed the medical records of patients without inherent factor deficiencies who received rFVIIa to limit hemorrhage following CHS at Children's National Health System in Washington, DC between April 2004 and June 2012. The data recorded were: age, weight, sex, type of cardiac defect, type of operation, risk adjustment for congenital heart surgery (RACHS) score, CPB time, aortic cross clamp time, rFVIIa dose(s), and type and amount of blood product transfusion. A total of 16 consecutive CHS patients who received rFVIIa either intra or postoperatively met the inclusion criteria for this series. The patients were grouped based on in-hospital mortality and the occurrence of MNE. A major neurological event was defined as a severe thrombosis-related neurologic complication, which was confirmed by computed tomography, magnetic resonance, or ultrasound imaging studies.

The operative CPB circuit utilized for all patients was primed by Plasmalyte A (Baxter, Deerfield, IL) with the addition of up to one unit of fresh frozen plasma (FFP) and packed red blood cells (PRBC) (depending on the blood volume of the patient) to obtain a hematocrit of 30% at initiation of CPB. Anticoagulation was achieved with an initial bolus of 2 mg/kg of heparin in patients below 30 kg and 3 mg/kg in patients above 30 kg. The adequacy of heparin administration was assessed by activated clotting time (ACT), and supplemental heparin was administered when needed to maintain an ACT above 480 s during extracorporal circulation. Cardiopulmonary bypass was established using a roller pump (Century Heart Lung Machine, Salyer PRN Biomedical, St. Louis, MO) and a Terumo Capiox®FX05 oxygenator with integral arterial filter (Terumo Corporation, Tokyo, Japan). During CPB, pH stat CO_2 management was utilized, and the hematocrit level was maintained around 30% with the use of a hemoconcentrator (Hemocor HPH®, Minntech, Minneapolis, MN) or by using PRBCs. The use of deep hypothermia and reduced flow bypass varied according to the procedure performed. After CPB,