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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,

heparin was reversed with protamine, with a dose of 1.3 times the initial heparinization dose in mg. Additional protamine doses were given to achieve an ACT below 120 s or lower than preoperative levels.

For patients requiring postoperative ECMO support, heparin reversal with protamine was not performed, and ACT levels were kept between 180 and 220 s with heparin infusion. In all patients, prothrombin time (PT)/partial thromboplastin time (PTT)/international normalized ratio (INR) as well as hematocrit and platelet counts were checked frequently to determine the need for blood product administration.

Results

For the 16 patients in the study, the demographics, type of surgery, and operative variables are summarized in Table 1. Median age at surgery was 6.8 months (range: 3 days–42 years). Six patients (38%) underwent single ventricle surgical palliation while the remaining ten patients (62%) had biventricular surgical repair. Seven patients (44%) survived to hospital discharge and nine (56%) died. The causes of mortality included MNE ($n = 4$, 44%), uncontrolled bleeding ($n = 3$, 33%), and sepsis ($n = 2$, 23%). Eight patients received rFVIIa intraoperatively while the remaining eight patients received rFVIIa postoperatively. The median cumulative rFVIIa dose administered was 97 mcg/kg (interquartile range, IQR: 89–262 mcg/kg). The median cumulative amount of blood products administered was 452 ml/kg (IQR: 190–807 mcg/kg). Fifty percent (8/16) of patients required ECMO support following CHS. Of these patients, 25% (2/8) survived to hospital discharge.

Major neurological events and in-hospital mortality are shown in Table 2. Compared to non-MNE patients, the MNE patients received a larger cumulative dose of rFVIIa (314 mcg/kg versus 94 mcg/kg) and a larger amount of cumulative blood products. Four of 16 patients who experienced MNEs died. The cause of death in two of these four patients was bilateral carotid artery thrombosis following rFVIIa administration. Both patients required ECMO support. When comparing survival to hospital discharge and in-hospital mortality (Table 2), the cumulative rFVIIa dose and amount of cumulative blood products were more uniform. However, a higher percentage of patients with in-hospital mortality received rFVIIa postoperatively.

Discussion

The first off-label use of rFVIIa as a rescue treatment for intractable postoperative bleeding was reported in 2001 [9]. In our center, the first off-label use of rFVIIa occurred in 2004 when published data regarding the use and dosing of rFVIIa in neonates and infants after cardiac surgery were scarce. As more data have become available,

Table 1. Characteristics and outcomes of the study cohort.

Pt	Sex	Age	Surgery type	Weight (kg)	Cumulative recombinant factor VIIa (mcg/kg)	RACHS score	ECMO	CPBT (min)	CCT (min)	CAT (min)
1[b]	F	21D	Biventricular Repair	2.3	100	3	Y	62	–	–
2	M	3D	Single Ventricle Palliation	2.3	178	6	N	158	–	39
3[b]	M	11D	Biventricular Repair	2.5	88	6	N	131	–	45
4[a,b]	F	13D	Biventricular Repair	2.6	94	2	Y	150	32	32
5	F	14D	Biventricular Repair	2.7	50	2	N	118	67	–
6[b]	F	13D	Single Ventricle Palliation	2.9	93	2	Y	75	–	46
7[b]	M	12D	Single Ventricle Palliation	3.0	60	3	Y	–	–	–
8	M	7M, 17D	Biventricular Repair	7.0	93	2	Y	133	–	–
9	F	6M	Single Ventricle Palliation	7.0	143	2	N	84	49	–
10[a,b]	M	2Y, 10M, 18D	Biventricular Repair	9.1	356	4	Y	261	6	9
11[b]	F	3Y, 2M, 30D	Biventricular Repair	10.0	100	4	Y	189	103	–
12	F	10Y, 7M, 2D	Biventricular Repair	27.0	253	3	Y	224	104	–
13	M	31Y, 8M, 20D	Biventricular Repair	51.0	265	2	N	218	33	–
14	F	41Y, 2M,11D	Biventricular Repair	52.8	95	3	N	216	67	–
15[a,b]	M	22Y, 4M, 8D	Single Ventricle Palliation	55.0	273	3	N	255	–	4
16[a,b]	M	36Y, 11M,15D	Single Ventricle Palliation	82.0	49	3	N	175	–	–

RACHS, risk adjustment for congenital heart surgery; IHM, in-hospital mortality; ECMO, extracorporeal membrane oxygenation; CPBT, cardiopulmonary bypass time; CCT, cross clamp time; CAT, circulatory arrest time.

[a] Major neurological event.

[b] In-hospital mortality.

Table 2. Comparison of variables according to presence or absence of a major neurological event and between survivors and in-hospital non-survivors.

Variable	No MNE (n = 12)	MNE (n = 4)	Survivors (n = 7)	Non-Survivors (n = 9)
Age, d	3 (1–107)	154 (9–405)	8 (1–386)	1 (0–155)
Weight, kg	5.0 (2.6–22.8)	32.1 (4.2–75.3)	7.0 (2.7–51.0)	3.0 (2.5–32.5)
RACHS score	3 (2–6)	3 (2–4)	2 (2–6)	3 (2–6)
Male gender	5 (42%)	3 (75%)	3 (43%)	5 (56%)
Single ventricle	5 (42%)	2 (50%)	2 (71%)	5 (56%)
ECMO	6 (50%)	2 (50%)	2 (29%)	6 (67%)
Cumulative products				
rFVIIa, mcg/kg	93.9 (87.8–169.0)	314.4 (138.6–491.5)	142.9 (92.9–253.0)	93.8 (87.9–314.4)
PRBC, ml/kg	277.6 (135.8–400.5)	493.2 (63.8–1272.8)	223.3 (66.6–350.4)	354.3 (124.2–1144.0)
FFP, ml/kg	52.5 (27.8–122.9)	177.4 (29.7–309.0)	44.6 (28.8–148.9)	68.5 (18.8–199.4)
Platelets, ml/kg	47.2 (21.3–95.8)	106.6 (12.8–258.4)	43.9 (16.4–70.4)	96.8 (22.6–202.6)
Cryoprecipitate, ml/kg	5.7 (2.2–11.6)	19.1 (2.0–37.9)	4.3 (2.3–8.6)	10.3 (1.9–34.9)
Postoperative rFVIIa	4 (33%)	4 (100%)	1 (14%)	7 (78%)

Continuous data are median (interquartile range); RACHS score, median (full range).

concerns have increased at our institution and elsewhere about proper rFVIIa dosing and the potentially higher risk of thrombotic MNEs, since MNEs are known complications in the cardiac surgery literature [10].

The standard bolus dosing of rFVIIa for hemophilia is 90 mcg/kg administered via intravenous bolus infusion every two hours until cessation of bleeding is noted [3]. This pharmacological dosing strategy is based on rFVIIa's mechanism of action to control bleeding that includes both a TF-dependent process and the generation of factor Xa and IXa on the surface of activated platelets unrelated to TF. The dosing frequency is every two hours as the drug half-life is 2.9 h in adults [11].

There is no clear consensus on the appropriate therapeutic dose of rFVIIa to address postoperative bleeding. In a study including non-cardiac postoperative patients, Friederich et al. utilized rFVIIa dosing of 20 mcg/kg and demonstrated that it was effective [12]. In another study involving postoperative CHS patients, Karsies et al. noted that 62% of patients responded to one dose and 29% responded to two doses of rFVIIa with an amount of 43 ± 22.9 mcg/kg per dose [8]. The authors concluded that administering 30–50 mcg/kg per dose every two to four hours would be effective. In our study, the median cumulative dose of rFVIIa utilized was 97 mcg/kg. In part, this stems from nearly half of our patient cohort undergoing rFVIIa administration while on ECMO support, wherein much less is known regarding therapeutic dosing.

The appropriate dosing regimen becomes more complex when considering patients who are on ECMO support following cardiac surgery. The pro-coagulant nature of rFVIIa in the context of exposure to non-endothelialized surfaces during ECMO support likely results in activation of circulating platelets [5]. In addition, studies have demonstrated that monocytes retrieved from oxygenators of CPB systems express TF [6]. Taken together, both serve as templates for rFVIIa-initiated thrombin generation, leading to ECMO circuit clotting and possible disseminated intravascular coagulation following rFVIIa administration [5,13]. In our case series, 50% (2/4) of patients who sustained MNEs were on ECMO support, and 75% (6/8) of patients on ECMO support expired.

The 25% observed rate of MNEs was higher than the rate of adverse thromboembolic events reported in other studies [14,15]. In our cohort, two of the four MNE patients who died experienced acute bilateral carotid artery thrombosis following rFVIIa administration. Although thromboembolic events have been well-described as complications of treatment with rFVIIa [10,14,16,17], acute bilateral carotid artery thrombosis is uncommon in the published literature [18,19]. Only one case of acute bilateral carotid artery thrombosis in a cardiac surgery patient following rFVIIa use has been reported [20]. In our series, bilateral carotid artery thrombosis was diagnosed with the use of head computed tomography scanning and head ultrasound imaging with Doppler.

This case series does have several limitations. Due to its retrospective design, unmeasured confounding factors may have contributed to the clinical outcomes that were observed. In addition, even though this is solely a descriptive case series, as the sample size is small and the results are from a single institution, the observed outcomes may not be applicable to other clinical settings.

Conclusions

This case series highlights the need for a prospective, multi-center trial with an adequate number of patients to sufficiently power the study to further delineate the relationship between rFVIIa doses and adverse clinical outcomes following rFVIIa use for bleeding after CHS.

Disclosure/funding statement

The authors did not receive any financial support for the study and declare that they have no conflict of interest.

Institutional review board (IRB) approval

This study was approved by the Institutional Review Board (IRB) of Children's National Health System in Washington, DC, United States.

Study limitations

Due to its retrospective design, unmeasured confounding factors may have contributed to the clinical outcomes that were observed in this study. In addition, even though this is solely a descriptive case series, as the sample size is small and the results are from a single institution, the observed outcomes may not be applicable to other clinical settings.

Study recommendation

This case series highlights the need for a prospective, multi-center trial with an adequate number of patients to sufficiently power the study to further delineate the relationship between rFVIIa doses and adverse clinical outcomes following rFVIIa use for bleeding after congenital heart surgery.

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