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Use of Factor VIIa and Anti-inhibitor Coagulant Complex in Pediatric Cardiac Surgery Patients

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OBJECTIVES Postoperative bleeding is a common cause of morbidity and mortality in cardiac patients who undergo cardiopulmonary bypass (CPB). Pediatric patients are especially at risk for adverse effects of surgery and CPB on the coagulation system. This can result in bleeding, transfusions, and poor outcomes. Excessive bleeding unresponsive to blood products can warrant the off-label use of recombinant activated clotting factor VIIa (rFVIIa) and/or anti-inhibitor coagulant complex (FEIBA). Several studies have shown the utility in these agents off-label in patients who have undergone cardiac bypass surgery with acute bleeding episodes that are refractory to blood products. However, data regarding use of these agents in pediatrics are sparse. The purpose of this study is to report the use of rFVIIa and FEIBA in pediatric cardiac surgery patients in our institution.

METHODS This was a retrospective chart review of pediatric cardiothoracic surgery patients who received rFVIIa or FEIBA at Children's Healthcare of Atlanta during the study period.

RESULTS Thirty-three patients received rFVIIa and 9 patients received FEIBA either intraoperatively or postoperatively for bleeding related to the cardiac procedure. Approximately 13% of rFVIIa patients and 55% of FEIBA patients required repeat doses. There were decreases for all blood products administered after rFVIIa and FEIBA were given. However, the doses used did not correlate with either positive or negative outcomes. Seventeen percent (n = 7) of rFVIIa patients experienced a thrombus and 22% (n = 2) of FEIBA patients experienced a thrombus.

CONCLUSIONS Both rFVIIa and FEIBA reduced blood product usage in pediatric patients following cardiac procedures.

ABBREVIATIONS CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FDA, US Food and Drug Administration; FEIBA, factor eight inhibitor bypassing activity (anti-inhibitor coagulant complex); FFP, fresh frozen plasma; pRBCs, packed red blood cells; rFVIIa, recombinant activated clotting factor VIIa; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery

KEYWORDS anti-inhibitor coagulant complex; blood transfusion; cardiovascular surgical procedures; pediatric; recombinant FVIIa

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Introduction

Postoperative bleeding is a common cause of morbidity and mortality in cardiac patients who undergo cardiopulmonary bypass (CPB). Pediatric patients are especially at risk for adverse effects on the coagulation system following surgery and/or CPB.[1] These effects can result in bleeding, the need for transfusions, and poor outcomes. These risks are inversely proportional to the patient's weight and can be attributed to hematological immaturity, coagulation defects associated with congenital heart disease, bypass equipment, and the nature of congenital heart surgery.[1] Excessive postoperative bleeding in adult cardiac surgery is associated with poor postoperative outcomes.[1] Perioperative blood transfusion in pediatric patients following cardiac surgery is associated with increased duration of mechanical ventilation and pediatric cardiac intensive care unit stay.[2] Although postoperative bleeding is routinely managed with blood product transfusions, and correction of coagulopathy, excessive bleeding unresponsive to blood products can warrant the off-label use of procoagulant medications, including recombinant activated clotting factor VIIa (rFVIIa; NovoSeven RT, Novo Nordisk, Plainsboro, NJ) and/or anti-inhibitor coagulant complex (FEIBA; FEIBA NF, Baxter Healthcare Corporation, Westlake Village, CA).

rFVIIa is approved by the FDA for the treatment of patients with hemophilia A or B with inhibitors, congenital factor VII deficiency, Glanzmann thrombasthenia, and acquired hemophilia.[3] FEIBA is approved by the FDA for the treatment of patients with hemophilia A or B with inhibitors.[4] Several studies[5–10] have shown the effectiveness of these agents off-label in patients who

have undergone cardiac bypass surgery with acute bleeding episodes that are refractory to the administration of blood products. However, data regarding use of these agents in the pediatric population are sparse.

The purpose of this study is to report the use of rFVIIa and FEIBA in pediatric cardiac surgery patients at our institution and describe dosing and clinical outcomes in these patients who have undergone cardiovascular surgery with refractory bleeding.

Methods

This study was a retrospective chart review of patients who had cardiothoracic surgery and received rFVIIa or FEIBA at the Egleston campus of Children's Healthcare of Atlanta during the period mentioned below. The Children's Healthcare of Atlanta Institutional Review Board approved this study, and the requirement for written informed consent was waived. Pharmacy charge data for rFVIIa and FEIBA were used to capture patient experiences. rFVIIa patient data were collected from the period of December 2015 to May 2016, whereas FEIBA patient data were collected from December 2015 to May 2017. The dates for patients who received rFVIIa were chosen based on a precompleted medication use evaluation. There were not enough FEIBA patients during this period, thus the time period was extended to capture additional FEIBA patients.

Patients who were ≤18 years of age were included if they had cardiothoracic surgery and received rFVIIa and/or FEIBA in the operating room and/or within 24 hours postoperatively. Patients were excluded if they had known or acquired thrombophilia or hemophilia disorders.

Descriptive summary statistics, overall and stratified by hemostatic agent, were calculated for patients' demographic, clinical characteristics, and product administration. Procedure type, location (e.g., operating room, unit), CPB time, shunt type, and dose (units/kg for FEIBA and mcg/kg for rFVIIa) for each hemostatic agent were collected. Before and after use of blood products (i.e., packed red blood cells [pRBCs], fresh frozen plasma [FFP], platelets, cryoprecipitate) and dose per kilogram of body mass were collected. The time period of 3 hours after administration of the product was chosen based on the half-life of factor VIIa (which is in both rFVIIa and FEIBA). Thrombotic events were also recorded.

Continuous variables were summarized using median and 25th to 75th percentiles. Categorical variables were summarized using counts and percentages. Differences between FEIBA and rFVIIa groups were tested using Wilcoxon rank sum tests for continuous variables and χ^2 tests (or if cell counts were <5, Fisher's exact test) for categorical variables. To test the null hypothesis of no monotonic relationship between the before/after change in product and the hemostatic agent dose per kilogram, the Spearman rank correlation coefficient was used. All statistical analysis was conducted using SAS 9.4 (SAS Inc, Cary, NC), and a p value < 0.05 was considered statistically significant.

Results

Tables 1 and 2 show summary statistics, stratified by hemostatic agent. Forty-seven patients met inclusion criteria. rFVIIa was given to 29 patients and 9 patients received FEIBA. A total of 41 doses were reviewed in a total of 38 patients. Ten patients (34%) who received rFVIIa and 3 (33%) given FEIBA were female. The majority of patients (73%) who received rFVIIa were ≤ 1 year. Those who received FEIBA were more equally distributed among the 4 different age categories and hence had more diverse weights. Also, 55% (n = 16) of those who received rFVIIa were <5 kg. All patients were given rFVIIa or FEIBA intraoperatively or postoperatively for bleeding related to the cardiac procedure. Of note, 1 (11.1%) patient who received FEIBA underwent the Norwood procedure (Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery [STAT] 5), 9 (28.1%) patients who received rFVIIa underwent the Norwood procedure, and 3 (33.3%) patients who received FEIBA underwent a heart transplant (STAT 4). The median CPB time for the patients who received FEIBA was 244 minutes compared with the median time of those who received rFVIIa, which was 161 minutes (of note, 37 of the 47 patients underwent CPB). The median mechanical ventilation days were 5.7 days in the patients who received FEIBA compared with 4.4 days in the patients who received rFVIIa. One patient (11.1%) who received FEIBA was on extracorporeal membrane oxygenation (ECMO), and 3 patients (10%) who received rFVIIa were on ECMO.

The dosing used for rFVIIa ranged from 42 to 102 mcg/kg with half receiving doses larger than 90 mcg/kg. The dosing used for FEIBA ranged from 0.025 to 20 units/kg, but the most consistent dose used was 10 units/kg. Most doses were given during the procedure in the operating room (89% for FEIBA and 84% for rFVIIa). Repeat doses of rFVIIa and FEIBA were given to 13.2% and 55.6% of patients, respectively.

None of the patients who received FEIBA required repeat cryoprecipitate or FFP administration within 3 hours after FEIBA. Eight (25%) patients who received rFVIIa required repeat cryoprecipitate or FFP within 3 hours of rFVIIa administration. We found a decrease in administration of all blood products after administration of rFVIIa or FEIBA; however, there was no statistical significance. However, the doses used did not correlate with any positive or negative outcomes.

Within 3 hours of FEIBA administration, the median dose of cryoprecipitate, FFP, pRBCs, and platelets were 0, 0, 4, and 16.5 mL/kg, respectively. There was a statistical significant difference for pRBCs within 3 hours after FEIBA compared with rFVIIa (p = 0.0368).

Table 1. Summary of Patient Level Characteristic*

Parameter	FEIBA (n = 9)	rFVIIa (n = 29)	p value†
Female, n (%)	3 (33)	10 (34)	1.00
Age, median (25th, 75th), mo	5.5 (0.2, 158.5)	0.3 (0.2, 19.4)	0.27
Age, n (%)			0.44
Neonate (<30 days)	3 (33)	17 (59)	
Infant (30 days–1 yr)	2 (22)	4 (14)	
Child (>1–13 yr)	1 (11)	4 (14)	
Adolescent (>13 yr)	3 (33)	4 (14)	
Weight, median (25th, 75th), kg	7.2 (4.5, 40.9)	4.4 (3.4, 8.8)	0.06
Weight, categorized, n (%)			0.37
<5 kg	3 (33)	16 (55)	
5–20 kg	2 (22)	7 (24)	
>20 kg	4 (44)	6 (21)	
ICU length of stay, median (25th, 75th), days	13.0 (8.0, 20.0)	10.0 (6.0, 22.0)	0.85
Total dose, median (25th, 75th)	20 (9.1, 21.7)‡	91.7 (81.0, 97.2)§	<0.0001
CPB time, median (25th, 75th), min	244.5 (218.5, 258.5)	161.0 (136.0, 213.0)	0.0064
STAT category, n (%)¶	n = 10	n = 26	0.16
0	1 (11)	0	
1	1 (11)	0	
2	1 (11)	1 (4)	
3	0	4 (15)	
4	6 (67)	11 (41)	
5	1 (11)	10 (37)	
ECMO, n (%)	1 (11)	3 (10)	1.00
Mechanical ventilation, median (25th, 75th), days	5.7 (0.98, 8.63)	4.4 (2.04, 6.75)	0.72
Shunt, n (%)	2 (22)	11 (38)	0.46
Shunt type, if any shunt, n (%)	n = 2	n = 11	1.00
BT shunt	1 (50)	6 (55)	
Sano shunt	1 (50)	5 (45)	
Shunt clotting, if any shunt, n (%)	0	4 (36)	1.00
Product given location	n = 9	n = 32	0.38
Both	1 (11)	1 (3)	
Intraoperative	8 (89)	27 (84)	
Postoperative	0	4 (13)	

BT shunt, Blalock-Taussig shunt; CBP, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; FEIBA, anti-inhibitor coagulant complex; rFVIIa, recombinant activated clotting factor VIIa; STAT, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery

* Each procedure is counted a unique encounter.

† Wilcoxon rank sum tests for continuous variables or χ^2 tests (if cell counts were <5, Fisher's exact test) for categorical variables.

‡ units/kg.

§ mcg/kg.

¶ The categories range from Category 1, which includes surgeries with the lowest risk of death, to Category 5, which includes the highest risk of death.

The median doses of cryoprecipitate, FFP, pRBCs, and platelets within 3 hours for patients who received rFVIIa was 8, 21.5, 22, and 15.5 mL/kg, respectively.

Five patients (16%) who received rFVIIa experienced a thrombus, of which 1 patient received 48 mcg/kg, 1 patient received 56.7 mcg/kg, 2 patients received 83

Table 2. Summary of Outcomes at Procedure Level

Parameter	FEIBA (n = 9)	rFVIIa (n = 29)	p value
Cryo			
Received within 3 hr before product, n (%)	9 (100)	29 (91)	1.00
Dose within 3 hr before product, median (25th, 75th), mL/kg*	7.0 (6.0, 14.0)	15.0 (9.0, 21.0)	0.05
Received within 3 hr after product, n (%)	0	5 (16)	0.57
Dose within 3 hrs after product, median (25th, 75th), mL/kg*	—	8.0 (7.0, 8.0)	—
FFP			
Received within 3 hr before product, n (%)	3 (33)	20 (63)	0.15
Dose within 3 hr before product, median (25th, 75th), mL/kg*	7.0 (6.0, 17.0)	17.5 (11.0, 27.5)	0.07
Received within 3 hr after product, n (%)	0	6 (19)	0.31
Dose within 3 hrs after product, median (25th, 75th), mL/kg*	—	21.5 (8.0, 29.0)	—
pRBCs			
Received within 3 hr before product, n (%)	4 (44)	20 (63)	0.45
Dose within 3 hr before product, median (25th, 75th), mL/kg*	25.5 (14.5, 42.5)	44.0 (22.0, 76.5)	0.23
Received within 3 hr after product, n (%)	4 (44)	7 (22)	0.22
Dose within 3 hr after product, median (25th, 75th), mL/kg*	4.0 (1.0, 11.0)	22.0 (14.0, 33.0)	0.0368
PLTs			
Received within 3 hr before product, n (%)	9 (100)	30 (94)	1.00
Dose within 3 hr before product, median (25th, 75th), mL/kg*	25.0 (18.0, 29.0)	27.5 (13.0, 40.0)	0.62
Received within 3 hr after product, n (%)	2 (22)	12 (38)	0.69
Dose within 3 hr after product, median (25th, 75th), mL/kg*	16.5 (10.0, 23.0)	15.5 (8.0, 22.0)	0.93
Repeat blood product given after hemostatic agent, n (%)			
Cryo given before AND after	0	5 (16)	0.57
FFP given before AND after	0	5 (16)	0.57
pRBCs given before AND after	0	2 (6)	1.00
PLTs given before AND after	2 (22)	11 (34)	0.69
Any blood product repeated	2 (22)	13 (41)	0.44
Any blood product received (Cryo, FFP, pRBCs, or PLTs), n (%)			
Before	9 (100)	31 (97)	1.00
Within 3 hr after	6 (67)	17 (53)	0.71
Cryo or FFP, n (%)			
Before	9 (100)	29 (91)	1.00
Within 3 hr after	0	8 (25)	0.16
pRBCs/PLTs received, n (%)			
Before	9 (100)	31 (97)	1.00
Within 3 hr after	6 (67)	15 (47)	0.45
Thrombosis/clotting, n (%)	2 (22)	5 (16)	0.64

Cryo, cryoprecipitate; FEIBA, anti-inhibitor coagulant complex; FFP, fresh frozen plasma; PLT, platelet; pRBC, packed red blood cell; rFVIIa, recombinant activated clotting factor VIIa

* Only in those who received the blood product.

or 84 mcg/kg, and 1 patient received 102 mcg/kg. Two patients (22.2%) who received FEIBA experienced a thrombus. One of these patients received 3 repeat doses of 11, 11, and 20 units/kg. Another patient received 2 additional doses of 10 units/kg each. Most of these thromboses were shunt clots (see Tables 1 and 2).

Discussion

rFVIIa contains activated recombinant human coagulation factor VII, which activates the final step of the common coagulation pathway and ultimately leads to the formation of a fibrin clot.[3] The clinical efficacy of rFVIIa in decreasing re-exploration, chest tube output, and blood product administration after cardiac surgery requiring CPB has been well documented[5–7]; however, only a few case reports have reported clinical utility in pediatric patients.

FEIBA is an anti-inhibitor coagulant complex that contains nonactivated factors II, IX, and X and activated factor VII. FEIBA bypasses factor VIII by shortening the activated partial thromboplastin time of plasma with factor VIII inhibitor.[4] The efficacy of FEIBA in postoperative bleeding episodes in adult cardiac patients has been reported.[8–9] However, limited data exist in the pediatric population.

This report illustrates that the use of either rFVIIa or FEIBA allow for a reduction of FFP, cryoprecipitate, platelets, and pRBCs postcardiac surgery in pediatric patients. The initial study design included chest tube output to be collected prior to and after rFVIIa or FEIBA administration. However, this was difficult to assess because chest tubes are usually placed in the operating room often during the time patients initially received rFVIIa or FEIBA.

A case report from 2015 in Japan describes the use of rFVIIa in a 2.5-year-old patient requiring emergent reconstruction surgery of the right ventricle-pulmonary artery conduit. Following surgery, the patient was successfully weaned from CPB but required large amount of pRBCs due to active hemorrhaging (>40 mL/kg/hr) for 3 hours. Platelets, prothrombin time, activated partial thromboplastin time, and fibrinogen were all recorded prior to surgery and before and after the administration of rFVIIa. Five hours after administration of a single 100 mcg/kg bolus of rFVIIa, the coagulation parameters of the patient were comparable to presurgery levels.[11]

Egan et al[12] reported their use of rFVIIa in 6 pediatric cardiac surgery patients. All patients experienced excessive and persistent bleeding and were given a dose of 180 mcg/kg that was repeated 2 hours later. Hemostasis was achieved and no adverse events were noted by the authors.[12]

Razon et al[13] reported the use of rFVIIa after cardiac surgery in 5 pediatric patients who experienced excessive blood loss, refractory to conventional therapies. This study showed a reduction in blood loss, blood product consumption, and coagulation test results after the administration of 56 to 96 mcg/kg rFVIIa. None of these patients experienced adverse effects from rFVIIa.

Kylasam et al[14] reported their use of rFVIIa in pediatric cardiac surgery patients. Twenty-five out of 1010 children who underwent cardiac surgery during the study period received rFVIIa. Eleven patients received a one-time dose of 180 mcg/kg and 14 patients received 2 doses of 180 mcg/kg. Hemostasis occurred in all patients and none experienced adverse effects from rFVIIa.

Another retrospective matched case-control study examined the use of rFVIIa in pediatric patients after cardiac surgery. Twenty-five patients received rFVIIa at a mean dose of 70 mcg/kg, and these patients experienced a reduction in bleeding complications compared with the matched controls. No thrombotic complications were noted.[15]

In comparison with positive outcomes from rFVIIa, Long et al[16] reported limited efficacy from rFVIIa. They reviewed the use of rFVIIa in all pediatric patients on ECMO who had refractory bleeding. This report included 7 patients, none of whom had positive outcomes from the rFVIIa and 2 who had complications related to rFVIIa administration (decreased oxygenator efficiency and intragastric clot).

In 2009, Guzzetta et al examined the current literature collected by the Congenital Cardiac Anesthesia Society rFVIIa Task Force regarding the use of rFVIIa in pediatric cardiac surgery pediatric patients and found that its use is reasonable as rescue therapy in post CPB-surgery bleeding events that are massive and potentially life-threatening, and refractory to first-line therapies. The Task Force agreed on a dose of 90 mcg/kg/dose, which could be repeated 2 hours after the initial dose. This dosing recommendation was based on a literature review of 29 studies conducted by Warren et al[17] that found the average dose that correlated to efficacy was 93.2 mcg/kg. However, the authors of this study concluded that patients should be started on a lower rFVIIa dose of 40 to 60 mcg/kg.[17] The overall mortality rate between all applicable patients (n = 158) was 4.4%.[18] Caution is advised in patients who are high risk for thromboembolic events as it was reported at 20% through all studies.

In this report, dosing did not correlate with efficacy or with adverse effects. Fifty percent (n = 15) of patients who received rFVIIa were dosed at greater than 90 mcg/kg even though doses of 40 to 50 mcg/kg have been shown to be safe and efficacious for this indication.[5,19–23] Of the 4 patients who experienced a clot, 1 patient was dosed at 56 mcg/kg and the other 3 were dosed at 83 to 102 mcg/kg. Similar to previous studies, most patients received FEIBA dosed at 10 units/kg. One (33%) of the patients who had a thrombus was given multiple FEIBA doses; one of those doses was 20 units/kg. All patients did experience blood product reduction when FEIBA was used.

Notably, 100% of patients who received rFVIIa were only given 1 dose, whereas 22.2% (n = 2) of patients received 2 doses of FEIBA and 33.3% (n = 3) received 3 doses of FEIBA. The FDA-approved dose for the labeled indications for rFVIIa (besides congenital factor VII deficiency) is 90 mcg/kg, and the FDA-approved dose

for labeled indications for FEIBA is 50 to 100 units/kg. It is interesting to note that the patients who received FEIBA received relatively low doses, based on FDA-approved labeling, but also required multiple doses.

A retrospective study conducted by Maeda et al[24] examined the effect of low dose FEIBA on incessant bleeding in pediatric patients on mechanical circulatory support. Low dose FEIBA was defined as 10 units/kg, and patients were stratified based on how many doses were received. Results showed that chest tube output and blood product administrations were significantly reduced in patients who received FEIBA (n = 11), and there were no thrombotic events or device malfunctions that occurred.[24]

Balsam et al[8] conducted a retrospective review to look at the use of FEIBA and its efficacy in patients with postoperative bleeding, and found that patients who received FEIBA had significantly lower blood product use and decreased chest tube output. Similar to rFVIIa, FEIBA contains boxed warnings for thromboembolic events, thus, caution should be used when this agent is used off-label. A case report described a fatal intracardiac thrombosis, confirmed by transesophageal echocardiography, after FEIBA 50 units/kg was administered.[25]

One study compared the use of rFVIIa and FEIBA in adult cardiac patients. One hundred sixty-eight patients were evaluated retrospectively who received rFVIIa or FEIBA postcardiac surgery to manage postbypass bleeding. Sixty-one patients received rFVIIa and 107 patients received FEIBA, and both groups of patients had similar adverse effects and efficacy. There were no significant differences in the number of thromboembolic events, 30-day mortality, or rates of surgery revision. Neither group demonstrated a clear relationship between dosage and occurrence of thromboembolic events. The average total dose of rFVIIa administered was 90.5 ± 48.3 mcg/kg. The average total dose of FEIBA was 18.6 ± 12.4 units/kg. There were no statistically significant differences in the rate of reoperation secondary to bleeding between the groups. Postoperative blood transfusion was similar in both treatment groups; however, the rFVIIa group received more units of platelets than the FEIBA group (3.1 ± 3.8 versus 1.6 ± 2.7, $p < 0.01$). Eight clinically significant thromboembolic events (13.1%) were observed in the rFVIIa group and 13 (12.1%) in the FEIBA group.[26] Our study showed a slightly high number of thromboses, which could be related to the smaller sample size. We observed 7 (17%) thromboembolic events—5 (16%) in the rFVIIa group and 2 (22%) in the FEIBA group.

Limitations to this study include the small sample size and lack of power. It is also retrospective with numerous confounding variables that could not all be accounted for. Future prospective studies and randomized trials are needed to assess superiority or inferiority of rFVIIa and FEIBA in pediatric cardiac patients. Because several studies have reported clinical efficacy with lower rFVIIa doses, a standard lower rFVIIa should be used ; it should then be compared with a historical higher rFVIIa dose to compare efficacy and safety in the setting of a randomized controlled trial. Chest tube output could also not be assessed in this study due to several confounding factors. Future studies should characterize chest tube output reduction and comparison between these 2 products. Efficacy should also be examined through other clotting metrics (i.e., rotational thromboelastometry, thromboelastography. In addition, because patients who received FEIBA received a relatively low dose and some of these patients required multiple doses, future studies should examine the utility, safety, and efficacy of a slightly higher FEIBA dose. In conclusion, both rFVIIa and FEIBA resulted in a reduction in blood product use for all pediatric patients after cardiac procedures. Although this result was not statistically significant, we feel that it is clinically significant.

ARTICLE INFORMATION

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