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Use of Recombinant Factor VIIa (NovoSeven) in Pediatric Cardiac Surgery

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Abstract: Significant post-operative bleeding can be encountered in a small population of pediatric surgical patients requiring cardiopulmonary bypass (CPB). Recombinant factor VIIa (NovoSeven) has been advocated as a possible off-label rescue therapy for these individuals when conventional blood component therapy alone is inadequate. This study retrospectively evaluates rFVIIa administration for the treatment of severe bleeding in pediatric patients immediately after cardiac surgical procedures requiring CPB. The records of 15 patients receiving rFVIIa for excessive rates of bleeding refractory to conventional blood component therapy were studied. Blood product utilization, rates of blood loss, and evidence of pathologic sequelae were compared with matched historical controls in retrospective fashion. NovoSeven doses ranged from 76 to 282 μg/kg (group 1 <30 kg) and 26 to 956 μg/kg (group 2 >30 kg). Blood product administration patterns were not significantly different ($p > .05$) in the intensive care unit (ICU) between patient groups receiving rFVIIa and those not treated. Bleeding rates (mL/kg/h) for the first 2 hours after admission to the ICU remained statistically unchanged but were significantly increased for those time periods >3 hours in patients <30 kg treated with NovoSeven. Patients >30 kg did not exhibit statistical differences in the rate of bleeding or the administration of blood products compared with matched controls. A significant reduction in prothrombin time ($p = .001$) and partial thromboplastin time ($p = .02$) was noted in patients <30 kg receiving rFVIIa. There were no pathologic sequelae directly attributed to the administration of rFVIIa in any patients treated. Trends in the improvement of bleeding disturbances were noted in the ICU in patients <30 kg treated with rFVIIa, subsequent to blood component therapy. The rate of bleeding (mL/kg/h) was improved in patients <30 kg for the first 2 hours in the ICU. For individuals >30 kg, there was no apparent benefit from the administration of rFVIIa. **Keywords:** rFVIIa, recombinant factor VIIa, NovoSeven, cardiopulmonary bypass, pediatric. *JECT. 2008;40:241–248*

Postoperative bleeding continues to play a significant contributory factor in the morbidity and mortality rate of infants undergoing surgery with cardiopulmonary bypass (CPB) (1–9) Post-surgical re-exploration for bleeding may occur in as many as 6% of patients undergoing CPB procedures and is associated with increased overall risk to the patient (1–3,7,9–11). Bleeding diathesis is associated with CPB primarily because of the interaction of blood components with non-endothelial surface exposure of CPB circuitry and blood returned from pericardial suction (1,2,9–12). This blood has been shown to contain both tissue factor and tissue plasminogen activator, potentially leading to activation of both hemostasis and fibrinolysis (1,2,9,10,12).

Significant clinical bleeding is often characterized by a disturbance in hemostasis induced by the reduction in fibrinogen and coagulation activity, thrombocytopenia, abnormalities in platelet function, complement activation, or fibrinolysis directly attributable to CPB (1,2,9,10,12). Pediatric patients, until 6 months of age, have a unique propensity for severe uncontrolled hemorrhaging because of the immaturity of coagulation factors (II, V, VII, X, XI, and XII). Additionally, a dilutional coagulopathy caused by their small blood volume in comparison to the CPB pump prime and residual heparin effects caused by immaturity of hepatic and renal function may also be contributing factors (1,2,9,10,12).

Treatment for postoperative coagulation impairment continues to be directed blood component therapy; however, off-label use of recombinant factor VIIa (NovoSeven; Novo Nordisk, Copenhagen, Denmark) in this population has been described with success (1–9,13–15). Originally designated for use in the management of patients presenting with hemophilia type A– and B–induced inhibitors to fVIIa and fVIX, a growing body of published literature suggests that rFVIIa may be a useful adjunct in the treatment of postoperative bleeding in both adult and pediatric patients after CPB procedures (1–12).

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In an effort to assess our own off-label utilization of rFVIIa, we undertook this retrospective study to evaluate the efficacy and safety of NovoSeven in reducing postoperative blood loss in pediatric cardiac surgical patients requiring CPB who developed intractable bleeding despite conventional directed blood component therapy.

MATERIALS AND METHODS

This retrospective review was conducted with the approval of the University of Iowa Hospitals Institutional Review Board (IRB-O1 200,602,723). A database analysis of cardiothoracic surgical procedures showed 15 patients that underwent cardiac surgery and later received postoperative recombinant factor VIIa for the treatment of excessive bleeding refractory to the administration of conventional directed blood component therapy (group A). This population was selected from 328 admissions to the pediatric intensive care unit (PICU) from 2004 to 2006 and will serve as the basis of this study in evaluating the efficacy of rFVIIa in reducing blood loss after cardiac surgery requiring CPB. For historical comparison, a demographically similar cohort of cardiac surgical patients with bleeding diathesis treated with directed blood component therapy alone, and not receiving rFVIIa, were also studied (group B). Patients studied were further assigned to subgroups according to weight group 1 (<30 kg; $n = 11$) or group 2 (>30 kg; $n = 4$) for analysis. Anti-fibrinolytic drugs were not administered to the patients enrolled in this study.

Blood loss was determined to be severe if >4 mL/kg/h for at least 2 consecutive hours by institutional protocol. The decision to administer rFVIIa was made after initiation of departmental protocols to alleviate bleeding by conventional directed blood product therapy target goals: packed red blood cells (PRBC) to achieve a hemoglobin (Hgb) ≥12.0 g/dL, fresh frozen plasma (FFP) 10–15 mL/kg, fibrinogen ≥100,000 mg/dL, International Normalized Ratio (INR) <3.5, activated partial thromboplastin time (aPTT) <40 seconds, platelet administration (PLTS) 10 mL/kg, platelet count ≥100,000 k/mm^3, cryoprecipitate administration (2 pooled units) ~30–40 mL. If two consecutive blood component administrations in 1 hour did not improve hemostasis, rFVIIa was administered at a suggested dosing of 60–90 μg/kg. If, after 60 minutes, significant hemostatic improvement was not observed, a second loading dose of rFVIIa was administered, which could again be repeated after 60 minutes, for a total of three administrations in a 24-hour period. Dosing and frequency of rFVIIa administration was determined by institutional protocol (University of Iowa Hospitals Advisory Committee; Transfusion Subcommittee). NovoSeven doses for group 1A ranged from 76.2 to 282 μg/kg (mean, 166 ± 79 μg/kg) and for group 2A ranged from 26 to 956 μg/kg (mean, 286 ± 450 μg/kg).

Patient charts, operative records, and blood bank utilization records served as the primary data sources for this study. Collected demographic information included patient age, weight, body surface area (BSA), CPB time, aortic cross-clamp time, circulatory arrest times, lowest rectal temperature achieved during CPB, lowest arterial temperature reached during CPB, CPB time under hypothermic conditions, and rewarming time before separation from CPB. Data collected with regard to coagulation and hemostasis profiles of studied individuals included blood product administration before separation from CPB, blood product administration in the operative theater and ICU, rFVIIa dosing, admission and hourly rate of bleeding recorded in the ICU, and documented evidence of pathologic sequelae associated with the use of rFVIIa.

A paired, two-tailed t test was used to compare CPB time, aortic cross-clamp time, lowest rectal temperature achieved, and CPB time under hypothermic conditions of rFVIIa-treated individuals with non-treated individuals. A Wilcoxon signed rank test for paired samples was used to evaluate all other non-parametric data including demographic data, blood product administration by area, and intensive care unit laboratory values. An adjusted p value was calculated from t tests using the Bonferroni approach for hourly bleeding rate data established in the ICU. All statistical analysis was completed using SAS Statistical Software (Cary, NC).

All data are presented as the mean ±SD or median and interquartile range (Q1, Q3). Data were considered statistically significant for $p < .05$ in all cases.

RESULTS

Demographic Data

Demographic data for groups A and B are shown in Table 1. Demographic data for subgroups 1 (patients <30 kg) and 2 (patients ≥30 kg) are shown in Table 1. Patients were divided into two groups according to weight to eliminate inconsistencies in CPB component utilization, priming volumes, hypothermic CPB conditions, and differing blood product administration needs for the management of coagulopathy. Groups A and B were used to identify recombinant factor VIIa (rFVIIa) use (group A) and those not treated with rFVIIa (group B). Variables evaluated were considered to determine whether these groups were statistically similar with regard to common indicators known to influence coagulation parameters during CPB. Among these variables were age, BSA, weight, evidence of preoperative cyanosis, CPB time, aortic cross-clamp time, circulatory arrest times, lowest rectal temperature achieved during CPB, lowest CBP arterial blood temperature, time on CPB under hypothermic conditions, and time on CPB engaged in rewarming the patient to normothermic conditions.

Table 1. Demographic data (all groups).

Variable	Group 1A (n = 11) [mean ± SD or median (Q1, Q3)]	Group 1B (n = 11) [mean ± SD or median (Q1, Q3)]	p Value	Group 2A (n = 4) [mean ± SD or median (Q1, Q3)]	Group 2B (n = 4) [mean ± SD or median (Q1, Q3)]	p Value
Age (d)*	60.82 ± 99.09 20.0 (6, 49)	15.55 ± 18.76 8.0 (6, 15)	NS	5292.5 ± 471.21 5292 (4927, 5657)	4531.3 ± 2758 5885 (3117, 5945)	NS
BSA (m^2)*	.22 ± .06	.20 ± .03	NS	1.53 ± .22	1.58 ± .14	NS
Weight (kg)*	3.77 ± 1.74	3.29 ± .79	NS	51.25 ± 13.6	53.73 ± 8.22	NS
CPB time (min)†	170.9 ± 47.05 179 (145, 210)	197.0 ± 47.83 180 (173, 195)	NS	267.75 ± 111.1 235 (186, 349)	97.75 ± 16.94 90 (88, 107)	NS
Cross-clamp time (min)†	70.64 ± 35.32 82 (41, 104)	110.0 ± 28.36 111 (100, 124)	.009	137.75 ± 101.0 94.5 (79, 196.5)	34.25 ± 23.66 43 (18.5, 50)	NS
Circulation arrest time (min)*	22.64 ± 30.45 10 (.0, 46)	3.00 ± 9.0 .0 (.0, .0)	NS	9.75 ± 19.5 .0 (.0, 19.5)	.00 ± .00	NS
Lowest temperature rectal (°C)†	23.55 ± 5.70	20.27 ± 2.49	NS	25.0 ± 6.22	30.0 ± 2.94	NS
Lowest temperature arterial blood (°C)*	20.73 ± 7.18	16.64 ± 2.42	NS	21.75 ± 7.41	26.75 ± 4.11	NS
Time cool (min)†	105.55 ± 51.44 125 (45, 150)	110.82 ± 23.94 115 (89, 134)	NS	163.75 ± 100.6 140 (85, 242)	39.75 ± 24.35 35.5 (23.5, 56)	NS
Rewarm time (min)*	63.18 ± 39.63 50 (35, 76)	64.36 ± 23.04 61 (53, 75)	NS	122.5 ± 35.71 107 (100, 145)	52.25 ± 2.87 51.5 (50, 54.5)	NS

Group 1A, rFVIIa, <30 kg; group 2A, rFVIIa, >30 kg; group 1B, no rFVIIa, <30 kg; group 2B, no rFVIIa, >30 kg.
*Wilcoxon signed rank test for paired samples p value.
†t test paired p value.
NS, not significant.

Group 1: For group 1 data (<30 kg), there were no significant differences between groups 1A and 1B, with the exception of aortic cross-clamp time, which showed a highly significant (p = .009) increase in this time for group 1B.

Group 2: Group 2 demographic data showed no statistical differences with respect to any of the aforementioned variables.

Blood Product Administration Totals by Area of Administration

Data shown in Table 2 identify the specific types and amounts of blood products administered to patients during three operative and postoperative periods in an effort to assess the characteristics of the transfusion profiles for each group studied. Blood component therapy administration patterns were used to assess the effectiveness of treatment regimens and show historical transfusion norms for comparison.

Group 1: Group 1 data (Table 2) show that there were no statistical differences in directed blood component therapy administration between the treatment group (A) and the non-treatment group (B), with the exception of packed red blood cell concentrates (PRBCs) administered during extracorporeal circulation (p = .01). Blood product administration after the perioperative period in the ICU showed a non-significant, but reduced trend in the administration of blood components such as PRBCs, FFP, and platelets.

Group 2: All data points in group comparison (groups 2A and 2B) were statistically insignificant. Trends in product administration indicating an increased tendency for directed blood product administration in the treatment group (group 2A).

Hourly Rate of Bleeding (ICU)

Table 3 provides data for hourly rates of bleeding for the first 7 hours after admission to the ICU. A statistical summary is provided for each group comparing the previous bleeding rate with that of the next hour rate of bleeding. Additionally, a comparison of the rate of bleeding between groups (groups 1A and 1B, Table 4; groups 2A and 2B, Table 5) is provided to determine whether there are differences in the rate of bleeding between the treated (group A) and non-treated groups (group B).

Group 1: The hourly rates of bleeding for the first 2 hours on admission to the ICU (group 1A) were not statistically different from those on admission. For ICU after admission hours 3–7, there was a pronounced statistical difference in the rate of bleeding. These values (3–7 hours) were highly significant ($p \leq .0056$ to $p < .0007$), indicating a significant increase in bleeding was observed in that time period.

Group 1B did not exhibit a statistical difference between any time periods recorded. Further analysis between groups 1A and 1B indicated no statistical difference at any time period. Treatment with rFVIIa (group A) did not provide a statistically significant benefit in reduction in bleeding over historical control (group B) for the first 7 hours after admission Table 4.

Group 2: The hourly intensive care unit bleeding data for group 2 indicated no statistical differences within either group A or B for the 7 hours after admission to the ICU or among groups. This analysis provides evidence that the treatment group (group 2A) did not exhibit a

Table 2. Blood product administration by area.

Blood Transfusion Totals by Area of Administration	Group 1A (n = 11) [mean ± SD or median (Q1, Q3)]	Group 1B (n = 11) [mean ± SD or median (Q1, Q3)]	Wilcoxon p Value	Group 2A (n = 4) [mean ± SD or median (Q1, Q3)]	Group 2B (n = 4) [mean ± SD or median (Q1, Q3)]	Wilcoxon p Value
Product administration before separation from CPB						
PRBC (mL)	483.6 ± 130.8 560 (280, 560)	778.2 ± 279.6 780 (560, 840)	.01	70 ± 140 .0 (.0, 140)	75 ± 150 .0 (.0, 150)	NS
FFP (mL)	265.4 ± 3.41 265 (265, 265)	263.2 ± 20.3 262 (250, 274)	NS	66.0 ± 132.0 .0 (.0, 132)	.0 ± .0 .0 (.0, .0)	NS
Anesthesia administration in operative theater						
PRBC (mL)	300 ± 201.8 280 (120, 560)	356.4 ± 220 280 (280, 560)	NS	910.0 ± 925.1 560 (280, 1540)	.0 ± .0 .0 (.0, .0)	NS .053
FFP (mL)	194.8 ± 168.3 201 (55, 290)	152.3 ± 191.2 .0 (.0, 292)	NS	1374.5 ± 1215.4 1082.5 (610, 2139)	.0 ± .0 .0 (.0, .0)	NS .054
PLTS (mL)	139.2 ± 131.0 120 (70, 155)	82.5 ± 48.4 60 (50, 125)	NS	334.3 ± 334.8 271.5 (110, 558)	.0 ± .0 .0 (.0, .0)	NS
Cryo (mL)	14.6 ± 16.9 .0 (.0, 32)	7.0 ± 16.0 .0 (.0, .0)	NS	128.5 ± 182 64 (.0, 257)	.0 ± .0 .0 (.0, .0)	NS
ICU blood product administration						
PRBC (mL)	197.3 ± 149.2 210 (60, 330)	375.0 ± 361.2 280 (80, 490)	NS	2049 ± 2963 877 (317, 3780)	75 ± 150 .0 (.0, 150)	NS
FFP (mL)	43.9 ± 64.9 27 (.0, 60)	171.5 ± 188.9 90 (.0, 362)	NS	1373 ± 1937 625 (259, 2488)	120.8 ± 241.5 .0 (.0, 241)	NS
PLTS (mL)	32.7 ± 54.4 .0 (.0, 60)	51.5 ± 64.4 25 (.0, 90)	NS	416.3 ± 693.6 110 (.0, 832)	.0 ± .0 .0 (.0, .0)	NS
Cryo (mL)	21.6 ± 21.2 30 (.0, 40)	6.6 ± 14.8 .0 (.0, .0)	NS	56.8 ± 113.5 .0 (.0, 113)	.0 ± .0 .0 (.0, .0)	NS

Group 1A, rFVIIa, <30 kg; group 2A, rFVIIa, >30 kg; group 1B, no rFVIIa, <30 kg; group 2B, no rFVIIa, >30 kg.
Wilcoxon signed rank test for paired samples p value.
NS, not significant.

statistical increase or reduction in blood loss. These data further illustrate that the bleeding pattern of group 2A did not differ from that of the untreated group (group 2B; Table 5). The significance of these data is that the treatment did not provide a statistical advantage in reduction of blood loss compared with historical cohorts.

ICU Laboratory Values

A summarization of the ICU laboratory values are provided in Table 6. Collected coagulation profile data included prothrombin time (PT), partial thromboplastin time (PTT), and minimum and maximum patient laboratory values for lactic acid accumulation.

Group 1: There was a significant reduction in laboratory values (group 1A) with respect to PT (p = .001), PTT (p = .02), and minimum value of lactic acid (p = .002) in the ICU. A statistical level of significance was not achieved in the maximum value of lactic acid in the ICU.

Group 2: Group 2 data do not provide statistical evidence of improvement in any indices recorded. There were no statistical differences between the treatment group and the non-treatment group with respect to PT, PTT, and minimum or maximum value of lactic acid.

Pathological Sequelae Associated with the Utilization of rFVIIa

A Fisher exact test was used to determine whether a statistically significant degree of difference between groups (A and B) existed with regard to pathologic sequelae incurred during the hospitalization period for the primary operative procedure studied. There were no significant differences between groups 1A and 1B or 2A and 2B. Pathologic coagulation disturbances or other conditions resulting in morbidity or mortality such as thromboembolic complications, cognitive deficits (seizure, stroke), pro-thrombotic syndromes, or deaths were not noted in any of the treated (group A) individuals. Group B data indicated that three individuals in this group (1B) were identified as meeting these criteria.

DISCUSSION

The off-label use of recombinant Factor VIIa (NovoSeven) in the setting of pediatric cardiac surgery is gaining increasing attention as a potential rescue therapy for postsurgical bleeding diathesis. Although there are few prospective studies documenting the use of rFVIIa in these patients, a number of retrospective and observational studies have shown significant reductions in bleeding and directed blood component use after its administration (2–4,6,8,9,14,16,17). Originally approved by the Food and Drug Administration in 1999 for individuals suffering from hemophilia with inhibitors to FVIII and FIX, NovoSeven use in non-hemophiliac patients is considered an off-label application. Well-documented scientifically con-

Table 3. Hourly rate of bleeding (ICU).

Group	1-Hour Bleeding Rate (mL/kg/h)	2-Hour Bleeding Rate (mL/kg/h)	3-Hour Bleeding Rate (mL/kg/h)	4-Hour Bleeding Rate (mL/kg/h)	5-Hour Bleeding Rate (mL/kg/h)	6-Hour Bleeding Rate (mL/kg/h)	7-Hour Bleeding Rate (mL/kg/h)
Group 1A (n = 11)	1.88 ± 4.07	3.34 ± 3.78	5.15 ± 3.57	4.32 ± 2.92	5.90 ± 3.0	5.56 ± 3.24	6.64 ± 3.26
t statistic	NS	NS	.0056	.004	.0007	.0014	.0007
Group 1B (n = 11)	2.25 ± 1.91	3.03 ± 2.27	2.93 ± 2.6	3.52 ± 2.74	2.91 ± 2.61	1.97 ± 2.98	2.99 ± 3.07
t statistic	NS	NS	NS	NS	NS	NS	NS
Group 2A (n = 4)	6.52 ± 12.47	7.53 ± 10.87	8.81 ± 12.6	7.39 ± 12.1	8.14 ± 19.7	5.23 ± 20.0	4.51 ± 27.4
t statistic	NS	NS	NS	NS	NS	NS	NS
Group 2B (n = 4)	.06 ± .29	.45 ± .67	.41 ± .68	.48 ± .58	.57 ± .58	.71 ± .59	.45 ± .68
t statistic	NS	NS	NS	NS	NS	NS	NS

Group 1A, rFVIIa, <30 kg; group 2A, rFVIIa, >30 kg; group 1B, no rFVIIa, <30 kg; group 2B, no rFVIIa, >30 kg.
Values are mean ± SD. Wilcoxon signed rank test for paired samples p value.
NS, not significant.

Table 4. Nonparametric results of change in bleeding rates from comparisons between groups 1A and 1B.

Hourly Rate of Bleeding (ICU)*	Number of Subjects	Group 1A [median and interquartile range (Q1, Q3)]	Group 1B [median and interquartile range (Q1, Q3)]	p Value†
1 hour	22	–1.60 (–4.80, –.30)	–3.50 (–8.60, .00)	NS
2 hour	22	–4.50 (–6.00, –1.20)	–5.59 (–6.10, –1.50)	NS
3 hour	22	–4.40 (–6.85, –1.60)	–5.00 (–11.60, –1.50)	NS
4 hour	22	–4.75 (–7.14, –1.60)	–5.59 (–7.56, .00)	NS
5 hour	16	–4.80 (–7.75, –4.30)	–6.50 (–7.99, 2.60)	NS
6 hour	16	–4.80 (–7.14, –3.35)	–7.00 (–7.36, .20)	NS
7 hour	16	–6.90 (–8.10, –4.09)	–5.40 (–7.56, .90)	NS

Group 1A, rFVIIa, <30 kg; group 1B, no rFVIIa, <30 kg.
*Variable represents the difference in the bleeding rate at that time point from the baseline bleeding rate.
†p value adjusted using Bonferroni.
NS, not significant (p = 1.00).

Table 5. Nonparametric results of change in bleeding rates from comparisons between groups 2A and 2B.

Hourly Rate of Bleeding (ICU)*	Number of Subjects	Group 2A [median and interquartile range (Q1, Q3)]	Group 2B [median and interquartile range (Q1, Q3)]	p Value†
1 hour	8	–1.880 (–3.750, –.750)	–.145 (–.270, .145)	.2128
2 hour	8	–2.900 (–4.960, –1.090)	–.240 (–.905, .015)	.7868
3 hour	8	–3.255 (–5.040, –.815)	–.215 (–.925, .100)	1.0000
4 hour	8	–2.985 (–5.690, –1.355)	–.455 (–.860, –.090)	.4242
5 hour	8	–2.810 (–4.950, –.860)	–.430 (–.925, –.205)	1.0000
6 hour	8	–2.805 (–4.185, .245)	–.710 (–1.175, –.235)	1.0000
7 hour	8	–2.830 (–5.375, –.605)	–.430 (–.915, .020)	1.0000

Group 2A, no rFVIIa, <30 kg; group 2B, no rFVIIa, >30 kg.
*Variable represents the difference in the bleeding rate at that time point from the baseline bleeding rate.
†p value adjusted using Bonferroni.

trolled studies are lacking, and as a consequence, basic information regarding dosing, efficacy, safety, and cost effectiveness of rFVIIa treatment regimens have relied on empirical and anecdotal evidence and personal experience. The mixed results of our study mirror the published experiences of others.

Demographic Makeup

Of the 328 cardiac surgery admissions to our PICU during the 2-year period from 2004 to 2006, 11 patients (<30 kg) received NovoSeven for refractory bleeding (group 1A). A demographically and numerically similar historical cohort (group 1B) was selected for comparison (Table 1). Among the variables identified to establish similarity between groups were age, weight, BSA, CPB/aortic cross-clamp time, bypass temperatures, and time spent in cooling and rewarming phases of CPB. Pediatric patients >30 kg (group 2) were evaluated separately because of differences in our directed blood component treatment algorithms, CPB circuitry needed, and CPB priming constituents. We identified four patients from our records in group 2A (>30 kg) that received rFVIIa. Of these variables, there were no statistically significant differences between groups 1A and 1B, with the exception of length of aortic

Table 6. ICU laboratory values.

ICU Coagulation and Lactic Acid Profile	Group 1A [mean ± SD or median (Q1, Q3)]	Group 1B [mean ± SD or median (Q1, Q3)]	*p* Value	Group 2A [mean ± SD or median (Q1, Q3)]	Group 2B [mean ± SD or median (Q1, Q3)]	*p* Value
Prothrombin time (s)	12.5 ± 2.01 13 (11, 13)	30.0 ± 24.95 22.5 (20, 27)	.001*	11.0 ± .82 11 (10.5, 11.5)	13.75 ± 1.5 14 (12.5, 15)	NS
Partial thromboplastin time (s)	52.5 ± 20.16 45 (37, 66)	89.1 ± 42.2 88 (46, 116)	.02†	45.75 ± 10.8 40.5 (40, 51.5)	46.3 ± 9.81 52 (35, 52)	NS
Minimum value lactic acid (mmol/L)	1.6 ± .89 1.4 (.8, 1.9)	4.35 ± 2.09 3.7 (2.6, 5.7)	.002*	2.53 ± 3.1 1.1 (.8, 4.25)	1.63 ± .64 1.9 (.9, 2.1)	NS
Maximum value lactic acid (mmol/L	6.57 ± 3.66 7.5 (3.2, 9.4)	12.6 ± 7.8 10.2 (7.4, 19)	NS	11.7 ± 12.2 6.05 (4.9, 18.55)	4.3 ± 2.5 5.5 (1.4, 6.0)	NS

Group 1A, rFVIIa, <30 kg; group 2A, rFVIIa, >30 kg; group 1B, no rFVIIa, <30 kg; group 2B, no rFVIIa, >30 kg.
*Wilcoxon signed rank test for paired samples *p* value.
†*t* test paired *p* value.
NS, not significant.

cross-clamp time ($p = .009$). There were no significant differences between groups 2A and 2B.

Although the number of patients identified in this study as having received rFVIIa was relatively small, a number of published reports cite similar percentages of the cardiac surgical population that went on to receive NovoSeven (3,6,18). To the degree possible, the historical cohort was identical to the study population in composition.

This study sought to elicit our own experience with utilization of rFVIIa in the context of bleeding by examining directed blood component therapy administration, rates of bleeding, and the potential for pathologic sequelae associated with its use.

Blood Product Administration/Efficacy

Blood product administration data (Table 2) identified the profiles of blood product administration in each group. The data provided by blood component therapy administration patterns were used to aid in the determination of the effectiveness of rFVIIa and show historical transfusion norms for comparison. Group 1 data, as one would expect, did not show significant differences in blood product utilization during CPB, with the exception of PRBC use ($p = .01$). Group 2 data (Table 2) did not exhibit any statistical differences during this time period. During the perioperative time of "anesthesia administration of blood products in the operative theater," no statistical differences existed between group 1 subjects with regard to blood product administration. On closer inspection, some trends signifying an increased proportion of blood component therapy aimed at restoring coagulation mechanisms, such as FFP, platelets, and cryoprecipitate, was apparent in group 1A who later received rFVIIa as a rescue therapy for bleeding. This trend was repeated in group 2, because a greater proportion of all factors were administered to group 2A. Although insignificant in both groups 1 and 2, the administration of blood components in the PICU (PRBCs, FFP, platelets) showed the reduced need for these products after administration of rFVIIa on arrival to the ICU in group 1A.

Hourly Rate of Bleeding in the ICU/Efficacy

Table 3 shows the rate of bleeding relative to baseline values subsequent to the administration of rFVIIa in the ICU. A non-significant difference in the bleeding rate for the first 2 hours in the ICU indicates the efficacy of rFVIIa in maintaining a static blood loss. As we move past 2 hours after administration of rFVIIa, there is a statistically significant increase at each time period through 7 hours. Karkouti et al. (19) reported similar findings of an increased tendency to re-bleed 120 minutes after administration of NovoSeven, possibly because of dilutional effects of blood product and other fluid administration. Assessment of group 2 did not show any significant differences at any time period, indicating that rFVIIa in these patients was relatively ineffective in immediately reducing blood loss. A trend for diminished rates of bleeding occurred at the sixth and seventh hours after administration of rFVIIa among these individuals. Examination of the rate of bleeding for the control groups 1B and 2B did not indicate a trend in either direction for the time points studied.

If we consider the statistical difference in the rate of bleeding between groups 1A and 2A (Table 4) and groups 1B and 2B (Table 5), we conclude that there are no statistical differences at any time point studied between groups. This again indicates a relative ineffectiveness of rFVIIa in producing an immediate reduction in the rate of bleeding.

ICU Laboratory Values

A number of published studies have reported a shortening of bleeding indices such as PT, PTT, and internal normalized ratio (INR) after the administration of rFVIIa (3,4,7,20) Findings of this study showed similar data. There was a significant reduction in laboratory values for PT ($p = .001$) and PTT ($p = .02$) in group 1A compared with historical controls in group 1B. Data examining lactic acid production in group 1A indicated a statistically significant reduction in minimum values. Although insignificant, the trend for the maximum value of lactic acid pro-

duction was likewise reduced in the rFVIIa-treated group. The significance of this finding is unclear; however, it is known that poor perfusion and acidosis (pH <7.2) render rFVIIa ineffective (4).

Safety

The creation of pathologic hypercoagulable states remain a concern with the administration of rFVIIa. NovoSeven is known to bind to activated platelets independent of tissue factor to activate factor X and enhance thrombin generation (4). Therefore, the threat of rFVIIa amplifying hemostasis in situations characterized by hemorrhage or impaired thrombin production may be real (4). In this study, we did not identify any pathologic sequelae resulting from the administration of rFVIIa, and there were no statistical differences between either groups 1A and 2A or groups 1B and 2B.

Cost Effectiveness

The successfulness of rFVIIa in reducing blood loss is well documented (4,6,8,17–19); however, its cost effectiveness has come under scrutiny because of its high cost (8,19). Our institutional acquisition price for rFVIIa is approximately $85.00/μg. Extrapolating, the estimated cost for a single treatment of rFVIIa (90 μg/kg) in a 7-kg infant is approximately $536.00; however, the product is provided in 1.2- and 4.8-mg vials costing $1020.00 and $4080.00, respectively, effectively increasing the cost of the treatment 52%. In our study, after administration of rFVIIa, the mean volume (mL) of PRBCs, FFP, cryoprecipitate, and platelets dropped in a statistically insignificant increment in the ICU (group 1A). However, if we calculate the mean differences in blood products administered, we find an average savings in blood components to be approximately $2000.00. Factoring out the increase in administered cryoprecipitate in this group, the overall savings is approximately $1550.00. If we consider the cost of the entire vial, the margin is reduced but still exhibits an overall savings of $530.00 per patient. The context of cost savings cannot be completely explained in monetary value, however. The degree of exposure to blood-borne pathogens is a legitimate concern for the clinician. Additionally, we must appreciate the circumstances of pathologic bleeding that preceded the administration of rFVIIa. Unfortunately, in group 2A, there were no such savings. From these data, we can conclude that rFVIIa was ineffective in reducing postoperative blood loss and imparted a substantial additional expense.

CONCLUSION

The use of rFVIIa in the off-label application of pediatric cardiac surgery requiring CPB and subsequent bleeding diathesis in this study seems to be no worse than cost neutral for those individuals <30 kg. Improvement in bleeding indicators such as blood products administered in the ICU, rate of bleeding in the ICU, and PT and PTT laboratory values were noted. Estimating the cost savings in blood product administration points toward a cost savings, but clearly more prospective randomized studies are needed to elucidate the value of rFVIIa compared with traditional methods of correcting pathologic post-surgical bleeds. Our study did not find an increase in morbidity or mortality associated with the use of rFVIIa, which suggests that it can be safely used in cases of catastrophic surgical bleed in individuals with refractory bleeding treated with conventional directed blood therapy. Pitfalls of this study are typical of all studies on the efficacy and safety of rFVIIa and include small numbers of patients and large SDs in variables studied, mixed case types, differing demographical makeup, and inconsistencies in dosing schedules. We suggest development of institutional protocols designed to proactively assess dose and monitor patients deemed highest risk. The pursuit of prospective investigational studies should be a priority for the cardiothoracic surgery community.

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