Original Article

Adequacy of Hemostatic Resuscitation Improves Therapeutic Efficacy of Recombinant Activated Factor VII and Reduces Reexploration Rate for Bleeding in Postoperative Cardiac Surgery Patients with Refractory Hemorrhage

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Abstract

Background: Excessive bleeding and surgical reexploration are common complications that increase the risk of multi-organ failure and prolonged hospitalization after cardiac surgery. Off-label use of recombinant activated factor VII (rFVIIa) is a recommended treatment for refractory bleeding. **Objective:** The objective of the study is to determine if the adequacy of hemostatic resuscitation enhances the efficacy of rFVIIa. **Methods:** This retrospective, observational, cohort study included patients who received rFVIIa for refractory postoperative bleeding after cardiac surgery. Patients were divided into two groups based on the presence or absence of adequate coagulation resuscitation before rFVIIa administration, defined as international ratio (INR) ≤1.5, platelet count ≥100 K/mL, and fibrinogen ≥200 mg/dL. The failure of rFVIIa treatment was defined as surgical reexploration within 24 h, thoracostomy drainage >400 mL/h within 6 h or transfusion of additional blood products or another rFVIIa dose within 6 h after initial rFVIIa dose. **Results:** Of the 3833 patients, screened who underwent cardiothoracic surgery procedures, 58 patients received rFVIIa for refractory postoperative bleeding. Successful hemostasis with rFVIIa was more likely in patients who were adequately resuscitated compared with those who were not (20 [71.4%] vs. 10 [33.3%], respectively; $P = 0.0046$). Multiple logistic regression analysis indicated that patients who were adequately resuscitated before rFVIIa were less likely to fail treatment (odds ratio, 0.16; 95% confidence interval [0.04–0.62]; $P = 0.007$). **Conclusions:** The therapeutic efficacy of rFVIIa is dependent on the adequacy of hemostatic resuscitation; restoration of normal serum fibrinogen, INR, and platelet counts >100 K/mL may provide an adequate substrate for rFVIIa to be effective in managing refractory postoperative cardiac surgical bleeding.

Keywords: *Cardiac surgery, coagulopathy, hemostasis, postoperative bleeding, recombinant activated factor VII, transfusion*

Introduction

Excessive bleeding and surgical reexploration are common complications that increase the risk of multi-organ failure and prolonged hospitalization after cardiac surgery.[1] Off-label use of recombinant activated factor VII (rFVIIa) is a recommended treatment for refractory bleeding when transfusion with autologous blood products is unsuccessful, but this intervention may also be associated with adverse thromboembolic events.[2-8] As a result, identifying specific patients in whom rFVIIa treatment would be most beneficial is an important objective. To date, only a few studies have examined the relationship between hemostasis before administration of rFVIIa and its subsequent efficacy in the setting of uncontrolled nonsurgical bleeding.[7,9-13] These data cumulatively suggest that at least partial correction of the underlying coagulopathy may be an essential determinant of the utility of rFVIIa for the treatment of refractory hemorrhage because a threshold amount of clotting factors and platelets is required for a normal coagulation response to occur. It is unclear whether more complete hemostatic resuscitation of coagulopathy than previously reported further improves the therapeutic efficacy of rFVIIa.[13] Accordingly, we tested the hypothesis that the adequacy of hemostatic resuscitation enhances the utility of rFVIIa and reduces

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reexploration rate in patients with uncontrolled bleeding after cardiac surgery.

Methods

This retrospective, observational, cohort study was conducted at Froedtert Hospital and the Medical College of Wisconsin, a 585-bed tertiary care academic medical center in Milwaukee, Wisconsin. The study was approved by the Medical College of Wisconsin Institutional Review Board. Written informed consent was waived because of the retrospective design. Consecutive patients who underwent cardiac surgery and received at least one dose of rFVIIa for refractory bleeding between July 1, 2013, and June 30, 2015, were eligible for inclusion. Patients were excluded if there was incomplete information available.

All data were extracted from the electronic medical record (Epic, Verona, WI, USA). Heparin reversal with protamine after cardiopulmonary bypass defined the start of data collection, which was then continued throughout the remainder of the intraoperative course and into the intensive care unit. All patients received intravenous epsilon-aminocaproic acid (10 g loading dose; 1 g/h infusion) during surgery. Transfusion was indicated when thoracostomy drainage exceeded 300 mL during the 1st h or was >400 mL during the first 2 h after arrival in the intensive care unit. Thresholds for transfusion are based on our usual practice and included packed red blood cells for hemoglobin concentration <7 g/dL, fresh frozen plasma for international ratio (INR) >1.5, cryoprecipitate for fibrinogen concentration <200 mg/dL, and apheresis platelets for platelet count <100 K/mL. Postoperative thromboelastography (TEG) monitoring during the study was variable and increasing throughout the study. A TEG-based treatment protocol was developed and implemented with variable adherence. The administration of additional protamine (based on activated clotting time >150, R-time heparin activity or empirically), epsilon-aminocaproic acid (based on TEG lysis % or empirically), prothrombin complex concentrate (based on INR or TEG), or desmopressin (based on TEG, known platelet dysfunction from drugs or renal failure or empirically) were at provider discretion.

Patients were divided into two groups based on the presence or absence of adequate hemostatic resuscitation defined as having all of the following: INR ≤1.5, platelet count ≥100 K/mL, and fibrinogen ≥200 mg/dL. Resuscitation was also deemed inadequate if transfusion of fresh frozen plasma, cryoprecipitate, platelets, an additional dose of rFVIIa, or another hemostatic agent (e.g., desmopressin, protamine, epsilon-aminocaproic acid, and prothrombin complex concentrate) was required after administration of the initial dose of rFVIIa.

Outcomes

The primary outcome was success or failure of rFVIIa to control refractory postoperative hemorrhage. The failure of rFVIIa treatment was defined as surgical reexploration within 24 h, thoracostomy drainage >400 mL/h within 6 h, or transfusion of additional fresh frozen plasma, cryoprecipitate, platelets, or additional rFVIIa within 6 h after administration of the initial rFVIIa dose. Secondary outcomes included units of transfused blood products, thoracostomy drainage, incidence of in-hospital thromboembolic events (including pulmonary embolism, deep venous thrombosis, pericardial thrombosis with or without tamponade, ischemic stroke, and myocardial infarction), and mortality.

Statistical analysis

The Anderson–Darling test was used to establish the normality of data distribution. Normally distributed continuous variables are presented as mean ± standard deviation and evaluated using Student's *t*-test. Data that are not normally distributed are expressed as median (interquartile range) and analyzed using the Mann–Whitney U-test. Categorical variables are presented as numbers with percentages and analyzed using Fischer's exact or Chi-squared tests. A multiple logistic regression analysis was used to determine factors that may impact the successful use of rFVIIa. Using a forward stepwise regression model, we evaluated the following covariates for inclusion: total and weight-based initial doses of rFVIIa, duration of cardiopulmonary bypass and aortic cross-clamping, fibrinogen concentration, temperature before rFVIIa, arterial pH before rFVIIa, total units of blood products transfused before rFVIIa, thoracostomy drainage during the 6 h before rFVIIa, and adequacy of coagulopathy resuscitation before rFVIIa. An alpha threshold of 0.1 was used to determine inclusion. Total units of blood products before rFVIIa, thoracostomy drainage 6 h before rFVIIa and adequacy of coagulopathy resuscitation were included in the final multiple logistic regression analysis. The null hypothesis was rejected when $P < 0.05$.

Results

Of the 3833 patients, who underwent cardiothoracic procedures, 67 patients received rFVIIa. Nine patients were excluded because of incomplete information, thus leaving 58 patients included in the final analysis. Demographics, the American Society of Anesthesiologists status, surgical procedures, and initial rFVIIa dose (5.1 ± 2.1 [65 ± 23 μg/kg] vs. 5.1 ± 2.0 mg [60 ± 20 μg/kg] in adequately vs. inadequately resuscitated patients, respectively) were similar between groups [Table 1]. The initial rFVIIa dose was more likely to produce successful hemostasis in patients who were adequately resuscitated based on the criteria compared

Table 1: Demographic, surgical, and transfusion data prerecombinant activated factor VII

	Adequate	Inadequate	*P*
n	28	30	-
Age (years)	57±13	58±16	0.70
Height (cm)	171±7	175±11	0.13
Weight (kg)	82±21	90±25	0.20
ASA status	4 (4-5)	4 (4-5)	0.64
Surgery type (*n*)			
CABG	1	1	>0.99
Single valve	6	4	0.50
Multiple valve	2	0	0.23
CABG/valve	3	4	>0.99
Aorta	9	10	0.59
Device implant	0	4	0.11
Transplant	7	7	>0.99
Emergency surgery (*n*)	13	14	>0.99
Device in place (*n*)	7	9	0.77
CPB (min)	246 (197-276)	214 (157-294)	0.57
Aortic cross clamp (min)	193 (130-222)	160 (126-221)	0.62
Circulatory arrest (*n*)	13	13	>0.99
rFVIIa dose (mg)	5.1±2.1	5.1±2.0	0.91
Blood products and labs pre rFVIIa			-
Red blood cells	3 (0-6)	3 (2-7)	0.77
Fresh frozen plasma	5 (3-8)	4 (2-8)	0.37
Cryoprecipitate	4 (1-5)	3 (1-4)	0.18
Platelets transfused	2 (2-4)	2 (0-3)	0.15
Total	14 (9-19)	14 (7-19)	0.52
Cell salvage (mL)	950 (435-5220)	1287 (741-1811)	0.3
Platelet count (1000/uL)	137 (106-184)	143 (100-171)	0.68
Fibrinogen (mg/dL)	231 (215-249)	238 (183-256)	0.85
Hemoglobin (g/dL)	8.8	9.5	0.14
Temperature (°C) before rFVIIa	36.4 (35.7-36.8)	35.9 (35.4-36.6)	0.10
pH (units) before rFVIIa	7.35±0.07	7.33±0.09	0.31

Data are mean±SD, median (interquartile range), or numbers. ASA: American Society of Anesthesiologists, CABG: Coronary artery bypass graft, CPB: Cardiopulmonary bypass, rFVIIa: Recombinant activated factor VII, SD: Standard deviation

with those who were not (20 [71.4%] vs. 10 [33.3%], respectively; $P = 0.0046$) concomitant with a markedly reduced requirement for surgical reexploration (1 [3.6%] vs. 11 [36.7%], respectively; $P = 0.0026$, [Table 2]). Thoracostomy drainage (390 [252–724] vs. 825 [495–1448] mL, respectively; $P = 0.0004$), the number of blood products administered (7 [1–11] vs. 10 [4–17], respectively; $P = 0.025$), and the total cost of resuscitation (14.1 [11.0–18.0] vs. 17.2 [13.9–21.3] thousands of dollars, respectively; $P = 0.044$) were also decreased in patients in whom the initial rFVIIa dose produced successful compared with unsuccessful hemostasis. In patients whom were inadequately resuscitated, 20 received additional protamine, 11 received desmopressin, 4 received epsilon-aminocaproic acid, and 3 received prothrombin complex concentrate after the initial rFVIIa dose. Multiple logistic regression analysis indicated that patients who were adequately resuscitated before administration rFVIIa were 6.25 times less likely to fail rFVIIa treatment compared with patients who were not (odds ratio, 0.16; 95% confidence interval [0.044–0.62]; $P = 0.007$, [Table 3]). No differences in thromboembolic events were observed between groups.

Discussion

The current results indicate that rFVIIa was more successful to treat refractory hemorrhage in patients after cardiac surgery when coagulopathy was adequately versus inadequately resuscitated. Not surprisingly, patients who had been adequately resuscitated before rFVIIa had less thoracostomy drainage and were less likely to return to the operating room for re-exploration. The current results are consistent with the previous literature. One study showed abnormalities in two or more TEG parameters predicted failure of rFVIIa to inhibit postoperative bleeding after cardiac surgery.[7] Prolonged prothrombin time was also identified as an independent predictor of rFVIIa failure in trauma patients with acute hemorrhagic shock.[9,10] The presence of a lower coagulopathy score (based on standard laboratory tests) was associated with a more favorable response to rFVIIa in 13 noncardiac surgery patients with

Table 2: Comparison of the effects of Recombinant activated factor VII in patients with adequate versus inadequate coagulopathy resuscitation

	Adequate	Inadequate	*P*
Treatment success (*n*)	20/28	10/30	0.0046
Surgical reexploration (*n*)	1	11	0.0026
Thromboembolic events (*n*)			
Pulmonary embolism	2	1	0.61
Deep venous thrombosis	1	1	>0.99
Pericardial thrombosis	1	1	>0.99
Gastrointestinal ischemia	1	0	0.48
Ischemic stroke	2	4	>0.99
Myocardial infarction	2	1	0.61
Total	9	8	0.78
Thoracostomy drainage (mL)	390 (252-724)	825 (495-1448)	0.0004
Blood products after rFVIIa (*n*)			-
Red blood cells	2 (0-3)	3 (1-8)	0.088
Fresh frozen plasma	0 (0-4)	3 (2-6)	0.013
Cryoprecipitate	1 (0-2)	1 (0-3)	0.53
Platelets	1 (0-2)	1 (0-3)	0.32
Total	7 (1-11)	10 (4-17)	0.025
Repeat rFVIIa (*n*)	3	6	0.47
Cost of blood products ($1000)	5.2 (3.3-7.1)	5.5 (3.4-6.9)	0.64
Cost of rFVIIa ($1000)	9.2 (6.2-11.9)	10.8 (8.9-15.8)	0.077
Total cost ($1000)	14.1 (11.0-18.0)	17.2 (13.9-21.3)	0.044
Mortality	3	6	0.47

Data are median (interquartile range) or *n*. rFVIIa: Recombinant-activated factor VII

Table 3: Multiple logistic regression analysis for failure of recombinant activated factor VII therapy

Variable	Coefficient	SE	OR	95% CI	*P*
Total blood products before rFVIIa	0.077	0.038	1.08	1.003-1.17	0.041
Thoracostomy drainage before rFVIIa	0.00089	0.00046	1.0009	1.0-1.0018	0.055
Adequacy of coagulopathy resuscitation	−1.81	0.68	0.16	0.044-0.61	0.007

rFVIIa: Recombinant activated factor VII, OR: Odds ratio, CI: Confidence interval, SE: Standard error

acute, uncontrolled bleeding.[11] Low serum fibrinogen concentration and thrombocytopenia were also suggested as risk factors for failure of rFVIIa to achieve hemostasis in a mixed cohort of cardiac and noncardiac surgery patients.[12] Patients with markedly abnormal coagulation tests (INR >2, thromboplastin time >60 s, fibrinogen concentration <100 mg/dL, and platelet count >80 K/mL) during refractory blood loss were less likely to respond to rFVIIa or to survive than their cohorts in a retrospective review of 18 Canadian cardiac surgery centers.[13] The findings emphasize that an adequate supply of coagulation factors (through the administration of autologous blood products) is necessary for rFVIIa to be an effective treatment for refractory nonsurgical bleeding. Indeed, an insufficient quantity or inhibition of coagulation factors, the presence of active fibrinolysis, or platelet dysfunction may partially attenuate or completely prevent the efficacy of rFVIIa. Notably, consumption or dilution of coagulation factors and acquired platelet dysfunction with or without thrombocytopenia are common during and after prolonged cardiopulmonary bypass.[14,15] Indeed, the bypass times observed in this study (median values of 246 and 214 min in adequately versus inadequately resuscitated groups, respectively; $P = 0.57$) were comparable to those that were previously associated with uncontrolled blood loss after cardiac surgery and were likely accompanied by these abnormalities.[13]

Similar amounts of rFVIIa were administered in each group suggesting that the success of rFVIIa treatment occurred independent of dose. Nevertheless, the dose of rFVIIa was not standardized but was left to the discretion of the attending intensivist in consultation with a critical care pharmacist. The ideal dose of rFVIIa for off-label treatment of refractory hemorrhage remains unclear, as doses ranging between 10 and 120 μg/kg have been previously reported.[4] Two small, single-center randomized clinical trials initially examined this controversy. Diprose *et al*. randomized 20 patients undergoing complex cardiac surgery to receive rFVIIa (90 μg/kg) or placebo.[16] The investigators showed that patients treated with rFVIIa received fewer blood products than those who did not. Gill *et al*. compared the effects of two doses of rFVIIa (40

and 80 μg/kg) to placebo on blood product utilization and thromboembolic events in cardiac surgery patients.[17] The results indicated that patients that received either dose of rFVIIa had lower transfusion requirements ($P = 0.01$) and were less likely to require surgical reexploration ($P = 0.03$). Patients who received rFVIIa may have sustained more frequent thromboembolic events including stroke in this study (placebo, 7%; 40 μg/kg, 14%, $P = 0.25$ vs. placebo; 80 μg/kg, 12%, $P = 0.43$ vs. placebo), but these numerical differences failed to reach the level of statistical significance.[17] The current findings demonstrated that the incidence of individual and total thromboembolic events was similar between adequately and inadequately resuscitated patients who received rFVIIa [Table 2], but whether rFVIIa increased thromboembolic events *per se* could not be determined because a placebo group was not included. Other studies and case reports supported the contention that doses of rFVIIa <90 μg/kg provided satisfactory hemostasis in cardiac surgery patients.[18-24] For example, Andersen *et al*. showed that an initial rFVIIa dose of 32 μg/kg (median value) caused a 50% reduction in postoperative transfusion requirements and eliminated the need for surgical reexploration without affecting the incidence of thromboembolic complications compared with placebo.[19] Similarly, Gelsomino *et al*. demonstrated that reductions in thoracotomy drainage, blood product transfusion, the duration of mechanical ventilation, and intensive care unit stay were observed in patients receiving 18 μg/kg of rFVIIa compared with propensity-matched controls who did not receive the medication.[21] Willis *et al*. analyzed data from 804 cardiac surgery patients in the Australia and New Zealand Haemostasis Registry and showed patients treated with 40 μg/kg or less of rFVIIa had similar rates of thromboembolic events, response to bleeding, and 28-day mortality compared with those who received 81–100 μg/kg.[25] A follow-up analysis from the same group indicated that a median rFVIIa dose of 91 μg/kg was used to treat critical bleeding in 3322 patients.[8] Thus, the rFVIIa doses of approximately 60 μg/kg used in the current investigation were most likely sufficient to stimulate hemostasis when adequate quantities of coagulation factors and platelets had been achieved. Nevertheless, it remains possible that a larger dose of rFVIIa may have successfully reversed refractory nonsurgical bleeding in patients who had been inadequately resuscitated in the current study.

The results of the current pilot investigation must be interpreted within the constraints of several other potential limitations. The retrospective experimental design has inherent shortcomings; the current findings require formal confirmation in a prospective, randomized, controlled trial. Because the current study is observational, only associations, but not strict cause-and-effect relationships, between the administration of rFVIIa and outcome variables can be identified. It is possible that a surgical source was the cause of the excessive bleeding, in which coagulant factors are not expected to be effective. Furthermore, it is possible that variances in hemostatic resuscitation were present and could not be controlled for as this was a retrospective review. Thromboembolic complications after administration of rFVIIa are well-known, but it is possible that some of these adverse events were overlooked in the current study because they were not prospectively identified.[4,5] The current investigation did not examine platelet activity and relied on platelet count to determine the adequacy of hemostatic resuscitation. The sample size using in the current study was most likely also not sufficiently powered to detect differences in thromboembolic events between groups. Finally, the current study did not include a control group in which rFVIIa was not administered.

Conclusions

The current results indicate that the therapeutic efficacy of rFVIIa is dependent on the adequacy of hemostatic resuscitation in postoperative cardiac surgery patients with refractory bleeding. Restoration of normal serum fibrinogen concentration decreases in INR <1.6, and reestablishing platelet counts >100 K/mL provided an adequate substrate for rFVIIa to be effective in many, but not all, patients with uncontrolled nonsurgical blood loss after cardiac surgery. This approach was also associated with decreases in thoracostomy tube drainage, risk for reexploration, and cost.

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Conflicts of interest

There are no conflicts of interest.

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