Intraoperative use of recombinant activated factor VII during complex aortic surgery

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Objective: Postoperative bleeding is a major cause of morbidity and mortality after complex aortic surgery. Intraoperative coagulopathy is a well-known culprit in this process. Recombinant activated factor VII is increasingly used for the postoperative management of such bleeding. We report our experience with the intraoperative use of this agent.

Methods: We performed a propensity-matched analysis on 376 retrospectively identified patients who underwent aortic root, arch, or ascending aortic replacement surgeries from 1999 to 2010. We matched a total of 58 patients: recombinant activated factor VII–treated group (n = 29) and nonrecombinant activated factor VII–treated group (n = 29). We compared the matched patients on re-exploration, mortality, bleeding-related events, use of blood and blood products, length of intensive care unit stay, duration of hospitalization, and thrombotic complications.

Results: Propensity-matched patients had similar preoperative and intraoperative characteristics. The mean dose of recombinant activated factor VII group was $23 \pm 12 \mu\text{g/kg}$. We found significantly lower rates of surgical re-exploration ($P = .004$), fewer prolonged intubations ($P = .004$), less total chest tube output ($P = .01$), and fewer units of packed red blood cells ($P = .01$) and fresh-frozen plasma ($P = .04$) transfused postoperatively in the recombinant activated factor VII group. There was no significant difference in mortality ($P = 1$), duration of intensive care unit stay ($P = .44$) or hospital stay ($P = .32$), or thrombotic complications between the groups ($P = .5$).

Conclusions: We recommend the intraoperative administration of low-dose recombinant activated factor VII but limited to the management of persistent, nonsurgical, mediastinal bleeding in aortic surgery. Further prospective randomized studies and larger cohorts are needed to verify these findings. (*J Thorac Cardiovasc Surg* 2012;143:1198-204)

Repair of aortic root, ascending aorta, and aortic arch aneurysms is associated with significant postoperative bleeding that often requires transfusion of large volumes of blood and blood products.¹ This is a well-known risk factor for postoperative morbidity and has been reported to cause an 8.1-fold increase in mortality rates.² In patients undergoing re-exploration for postoperative bleeding after cardiac surgery, it has been demonstrated that only 50% have a grossly identifiable surgical source of bleeding.³ This identifies microvascular bleeding caused by coagulopathy as a major risk factor for postoperative bleeding. Strategies to prevent coagulopathic bleeding are essential for the successful management of patients undergoing complex aortic operations.

Recombinant activated factor VII (rFVIIa; NovoSeven, NovoNordisk, Copenhagen, Denmark) was initially

developed for management of bleeding in hemophiliacs.^{4,5} Over the last decade, rFVIIa has been increasingly used in the postoperative management of intractable bleeding after cardiac and aortic surgery.⁶ Of note, the precise dose required to control bleeding without causing thrombotic complications is controversial.⁷ Dose recommendations in the current literature have ranged from 30 to 200 $\mu\text{g/kg}$, which can be administered in multiple doses.

Currently, there are a paucity of data regarding the intraoperative use of rFVIIa as a measure to minimize postoperative bleeding and associated complications.⁸ We report our clinical experience with off-label intraoperative use of low-dose rFVIIa for inadequate hemostasis in patients undergoing complex aortic repair procedures.

MATERIAL AND METHODS

Study Population

Patients were retrospectively identified from our aortic aneurysm research registry. From 1999 to 2010, 488 patients underwent repair of the aortic root, ascending aorta, and arch (Table 1). Excluded from the study were the patients undergoing concomitant coronary artery bypass grafting, mitral or tricuspid valve surgery, and congenital surgery. We further excluded patients who had abnormalities in the preoperative coagulation panel (prothrombin time, partial thromboplastin time, bleeding time, and platelet count [if $< 150 \text{ k/mL}$]). The above exclusion criteria narrowed the pool to 376 patients. In February 2009, we started administering

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Abbreviations and Acronyms

DHCA	= deep hypothermic circulatory arrest
FFP	= fresh-frozen plasma
ICU	= intensive care unit
POD	= postoperative day
PRBC	= packed red blood cell
rFVIIa	= recombinant activated factor VII

intraoperative off-label rFVIIa to patients who met our clinical criteria as outlined below. We identified 37 such patients. The remaining patients served as a control pool for the propensity-matched analysis.

Study End Points

The primary end points of our study were major bleeding requiring surgical re-exploration and postoperative in-hospital death. Secondary end points were the use of blood and blood products, delayed chest closure, postoperative tamponade, chest tube output, duration of intensive care unit (ICU) stay, prolonged intubation (>48 hours), duration of hospitalization, and any complication that might be related to thrombosis.

Data Collection

Preoperative and intraoperative data are listed in Table 2. The institutional review board approved the use of these data for the purposes of this study. All patients undergoing aortic surgery after 2009 were informed in advance that they might receive factor VII.

Surgical Technique

After endotracheal intubation and administration of appropriate anesthetic agents, radial arterial, central venous, and Swan-Ganz catheters were introduced per routine. Median sternotomy was performed followed by arterial and venous cannulations as outlined below. Standard cardiopulmonary bypass technique was carried out using membrane oxygenators. Of note, 152 patients (40%) received right axillary cannulation for arterial access. Venous access was obtained via cannulation of the right atrium or the femoral vein. Depending on the complexity of the procedure, moderate to deep systemic hypothermia was used. Mean arterial pressure was kept between 50 and 70 mm Hg during cardiopulmonary bypass. Myocardial protection was achieved by antegrade and retrograde cold blood cardioplegia. Heparin was administered to achieve an activated clotting time more than 480 seconds. This was neutralized with appropriate use of protamine administered within 10 minutes after the end of cardiopulmonary bypass. All patients received aminocaproic acid (AMICAR; Lederle Parenterals, Carolina, Puerto Rico) perioperatively. Generally accepted criteria were used for re-exploring patients with postoperative bleeding.⁹

Management of Intraoperative Bleeding

Figure 1 summarizes the algorithm we used to treat intraoperative bleeding. Beginning in February 2009, rFVIIa was added to this regimen as described below. If bleeding persisted after routine attempts at surgical hemostasis, coagulation parameters were measured to rule out any existing correctable measures. If none existed or corrected, rFVIIa was administered at 1 to 2 mg/dose (10–30 μ g/kg), which was repeated once if bleeding persisted. If the surgeon was not satisfied with the degree of hemostasis despite these measures, the chest was left open and packed with continuous negative pressure suction dressing for delayed closure. The patient was subsequently transferred to the ICU for observation and brought back to the operating room within 24 to 72 hours for definitive closure.

Statistical Analysis

Demographic, perioperative, and intraoperative continuous variables were compared using the unpaired or paired *t* test for the prematch and propensity-matched groups, respectively. Accordingly, dichotomous variables were compared using the Fisher exact or McNemar test.

Because of the absence of preoperative randomization, a propensity-matched analysis was performed.¹⁰ Propensity scores were generated through a logistic regression procedure using the following risk factors observed to be significant in the univariate prematch group comparisons and deemed likely to cause postoperative bleeding: gender, total body surface area, emergency status of the operation, total pump time, redo sternotomy, and use of deep hypothermic circulatory arrest (DHCA). Once generated, propensity scores were addressed as proposed by Austin.¹¹ Matching without the replacement method was used to pick up a match from the control group. Finally, patients were matched by an identical 5-digit propensity score. If this could not be done, we then proceeded to a 4-, 3-, 2-, or 1-digit match. Five-digit matches were 11, and 4-3-2-1 matches were 6, 6, 4, and 2, respectively. We were unable to match 8 patients who had rFVIIa; therefore, we excluded those from further analysis.

Values are expressed as mean $\pm$ standard deviation, median (minimum–maximum), or percentage. All analyses were performed with SPSS 13.0 software (SPSS Inc, Chicago, Ill).

RESULTS

Total Prematch Group

The mean age was 63 ± 13 years (19–88), and 64% were male. The mean intraoperative dose of rFVIIa in 37 patients was 23 ± 14 μ g/kg (10–60). Nineteen patients received 1 mg of rFVIIa (51%), 13 patients (35%) received 2 mg of rFVIIa, 4 patients (10%) received 3 mg of rFVIIa, and 1 patient (2%) received 4 mg of rFVIIa before leaving the operating room. Of note, none of the patients received additional doses of rFVIIa after leaving the operating room. The patient who required 4 mg of rFVIIa had had an acute type A dissection requiring replacement of the aortic root, arch, and ascending aorta. Furthermore, the patient was anticoagulated with argatroban because of a standing diagnosis of heparin-induced thrombocytopenia with a preoperative platelet count of $155 \times 10^3/\text{mL}$.

Prematch Comparison

All performed operations are listed in Table 1. The ascending aorta was involved in 195 patients (51%), the aortic root was involved in 94 patients (25%), and the aortic arch was involved in 105 patients (28%). Prematch baseline variables are shown in Table 2. In the prematch analysis, there were significantly more male patients in the control group ($P = .02$). The rFVIIa group had longer total pump time ($P = .008$) and aortic crossclamp time ($P = .006$). Redo sternotomy was performed in 10 patients (27%) in the rFVIIa group and in 39 patients (11%) in the control group ($P = .01$). Other preoperative variables were not statistically different.

Postmatch Comparison

The propensity-matched analysis yielded 58 patients available for analysis. All variables before administration of rFVIIa were similar between the 2 groups (Table 2).

TABLE 1. Performed operations (%)

	Before match			After match		
	Overall (n = 376)	rFVIIa (n = 37)	Control (n = 339)	Overall (n = 58)	rFVIIa (n = 29)	Control (n = 29)
Ascending ± arch ± AV repair	27 (7)	0	27 (7)	0	0	0
Ascending ± arch ± AV replacement	82 (21)	1 (2)	81 (23)	1 (2)	1 (3)	0
Ascending aorta replacement	101 (26)	4 (10)	97 (28)	7 (12)	3 (10)	4 (14)
Root repair + ascending	26 (6)	1 (2)	25 (7)	3 (5)	1 (3)	2 (7)
Root + ascending	31 (8)	6 (16)	25 (7)	11 (19)	5 (17)	6 (20)
Root repair + ascending + arch	4 (1)	2 (5)	2 (0.5)	4 (7)	2 (7)	2 (7)
Root + ascending + arch	33 (8)	9 (24)	24 (7)	13 (22)	7 (24)	6 (20)
Ascending + arch	58 (15)	14 (37)	44 (12)	17 (29)	10 (34)	7 (24)
Isolated arch	14 (3)	0	14 (4)	2 (3)	0	2 (7)

AV, Aortic valve; rFVIIa, recombinant-activated factor.

The mean intraoperative dose of rFVIIa was $23 \pm 12 \mu\text{g/kg}$ (10–55). Fifteen patients received 1 mg of rFVIIa (51%), 10 patients (34%) received 2 mg of rFVIIa, and 4 patients (13%) received 3 mg of rFVIIa before leaving the operating room. The rFVIIa group received significantly fewer units of packed red blood cells (PRBCs) (7 ± 2 vs 9 ± 4 , $P = .01$) and fresh-frozen plasma (FFP) (4 ± 1 vs 6 ± 2 , $P = .04$) in the postoperative period (Table 3). There was a tendency for the rFVIIa group to receive fewer units of single-donor platelets and cryoprecipitate, but these values did not reach statistical significance ($P = .097$ and $P = .091$, respectively).

Five patients (17%) underwent surgical re-exploration for bleeding in the rFVIIa group compared with 14 patients (48%) in the control group ($P = .004$). None of the re-explored patients had a surgical source of bleeding. One

patient (3%) in the rFVIIa group had postoperative cardiac tamponade (caused by excessive packing in a patient who underwent open chest surgery) compared with 4 patients (13%) in the control group ($P = .25$) (Table 3). Patients receiving rFVIIa had lower total chest tube output when compared with the control group ($810 \pm 376 \text{ mL}$ vs $1020 \pm 515 \text{ mL}$, $P = .01$, respectively). All patients had adequate hemostasis before chest closure; 7 patients had delayed chest closure, and mean chest closure time was 1.4 ± 0.7 days (1–3) after the initial operation. Two patients (6%) in the rFVIIa group and 5 patients (17%) in the control group had delayed chest closure ($P = .25$).

The median ICU stay was 2 days in the rFVIIa group (range, 1–7) compared with 3 days in the control group (range, 1–15). The rate of prolonged intubation was significantly lower in the rFVIIa group compared with the control

TABLE 2. Preoperative and operative characteristics of overall population and comparison between recombinant activated factor VII and control group before and after propensity match

Variable	Before match				After match			
	Overall (n = 376)	rFVIIa (n = 37)	Control (n = 339)	P value	Overall (n = 58)	rFVIIa (n = 29)	Control (n = 29)	P value
Age (y)	63 ± 13	59 ± 12	63 ± 13	.12	60.3 ± 12	60.3 ± 11	60.3 ± 13	.62
Gender (male, %)	244 (64)	18 (48)	226 (66)	.02	29 (50)	14 (48)	15 (51)	1
Body surface area (m^2)	1.83 ± 0.2	1.81 ± 0.1	1.84 ± 0.2	.3	1.82 ± 0.1	1.81 ± 0.1	1.82 ± 0.1	.98
Hypertension (%)	304 (81)	30 (81)	267 (78)	.46	46 (80)	24 (82)	22 (75)	.5
COPD (%)	87 (23)	10 (27)	77 (22)	.34	12 (20)	6 (20)	6 (20)	1
euroSCORE (%)	6.3 ± 3.2	6.5 ± 3.1	6.3 ± 3.2	.62	6.5 ± 3.1	6.7 ± 3.5	6.3 ± 2.7	.59
Renal dysfunction (%)	27 (7)	3 (8)	26 (7)	.56	5 (8)	2 (6)	3 (10)	1
Preoperative EF (%)	66 ± 13	64 ± 16	66 ± 12	.74	65 ± 13	65 ± 11	65 ± 14	.94
Emergency surgery (%)	72 (19)	6 (16)	66 (19)	.41	11 (18)	5 (17)	6 (21)	1
Acute dissection (%)	57 (15)	5 (13)	52 (15)	.49	7 (12)	3 (10)	4 (14)	1
Chronic dissection (%)	13 (3)	1 (2)	12 (3)	.62	1 (1)	0	1 (3)	1
Redo sternotomy (%)	49 (13)	10 (27)	39 (11)	.01	11 (18)	6 (21)	5 (17)	1
TPT (min)	196 ± 70	227 ± 65	193 ± 70	.008	212 ± 61	220 ± 64	203 ± 59	.17
ACC time (min)	133 ± 65	165 ± 76	132 ± 64	.006	135 ± 62	142 ± 73	128 ± 49	.23
DHCA (%)	267 (71)	25 (67)	242 (71)	.7	45 (77)	22 (75)	23 (79)	1

ACC, Aortic crossclamp time; COPD, chronic obstructive pulmonary disease; DHCA, deep hypothermic circulatory arrest; EF, ejection fraction; rFVIIa, recombinant activated factor VII; TPT, total pump time; euroSCORE, European System for Cardiac Operative Risk Evaluation.

FIGURE 1. Hemostasis management in aortic surgery. *ICU*, Intensive care unit; *INR*, international normalized ratio; *PTT*, prothrombin time; *PLT*, platelet; *rFVIIa*, recombinant activated factor VII.

group (27% vs 58%, $P = .004$). There was no difference in the length of ICU stay ($P = .44$) or duration of hospital stay ($P = .32$) between the groups (Table 3).

There were 6 thrombotic complications in 6 patients (10%) (Table 4). In the rFVIIa group, 1 patient had a stroke and 1 patient had a transient ischemic attack (7%). In the control group, 2 patients had a stroke, 1 patient had a transient ischemic attack, and 1 patient had a myocardial infarction. There was no statistically significant difference in the number of thrombotic events between the 2 groups ($P = .5$).

Overall 30-day mortality was 4 of 58 patients (6%), with 2 mortalities in each group. In the rFVIIa group, the first mortality occurred in a patient who had developed heparin-induced thrombocytopenia in addition to acute postoperative renal failure and concomitant sepsis after a re-operation of aortic root, arch, and ascending aortic replacement. This patient died on postoperative day (POD) 17. The second mortality also occurred in a patient who underwent a redo aortic root replacement for an infected mechanical valve. The coronaries were reimplemented using the Cabrol

TABLE 3. Postoperative blood and blood product use and bleeding-related complications in matched patients

	rFVIIa (n = 29)	Control (n = 29)	P value
Blood and blood product use			
PRBC (units)	7 ± 2	9 ± 4	.01
FFP (units)	4 ± 1	6 ± 2	.04
Platelets (single donor)	3 ± 2	4 ± 2	.097
Cryoprecipitate (units)	12 ± 2	14 ± 3	.091
Clinical bleeding-related complications			
Delayed chest closure (%)	2 (6)	5 (17)	.25
Postoperative tamponade (%)	1 (3)	4 (13)	.25
Re-exploration (%)	5 (17)	14 (48)	.004
Total average chest tube output (mL)	810 ± 376	1020 ± 515	.01
Hospital outcomes			
Median ICU stay (d)	2 (1–7)	3 (1–15)	.44
Prolonged intubation (%)	8 (27)	17 (58)	.004
ARDS	2 (6)	5 (17)	.25
Pulmonary infection	2 (6)	3 (10)	1
Duration of hospitalization (d)	9 ± 5	10 ± 7	.32
Mortality (%)	2 (6)	2 (6)	1

FFP, Fresh-frozen plasma; ICU, intensive care unit; PRBC, packed red blood cell; rFVIIa, recombinant activated factor VII; ARDS, acute respiratory distress syndrome.

technique. Sudden cardiac arrest developed in this patient on POD 5 from an episode of aspiration and subsequently died after failed attempts at resuscitation and a trial of extracorporeal membrane oxygenation. At the time of postmortem autopsy, the coronary interposition grafts were patent.

In the control group, the first death occurred from multi-organ failure on POD 14 in a patient who had undergone aortic root and ascending aortic replacement. This patient was re-explored on POD 2 for persistent mediastinal bleeding. The second death in this group occurred on POD 6 in a similar patient who had persistent postoperative bleeding requiring re-exploration. The patient eventually expired from overwhelming sepsis with subsequent cardiac and renal failure. The patient underwent repair of acute type A dissection with preoperative tamponade.

DISCUSSION

The development of an approach for the management of inadequate hemostasis due to coagulopathy after aortic

surgery is essential to have better outcomes.¹² Such management must start at the beginning of the operation to preserve the hemostatic system. Aprotinin has been widely used to reduce blood loss and blood transfusion requirements after thoracic aortic operations¹³; however, there is controversy on the use of aprotinin because of its reported side effects on renal function¹⁴ and mortality. In the post-aprotinin era, there is no consensus for any agent to reduce bleeding after aortic operations.

Despite its potential for increasing rates of thrombotic complications, rFVIIa has been shown to be effective in the management of uncontrolled bleeding after major operations.^{6,15–17} In several small randomized trials, postoperative administration of rFVIIa has been associated with fewer blood transfusions and lower mortality rates particularly if limited to therapeutic doses of 90 µg/kg.¹⁸ There currently exist no standardized criteria for the off-label use of rFVIIa intra- or postoperatively in cardiovascular surgery. To our knowledge, this study represents the largest report of intraoperative off-label use of rFVIIa in patients undergoing cardiothoracic surgery. A randomized trial also showed the efficacy of intraoperative use in only 10 patients with an rFVIIa dose of 90 µg/kg.¹⁹ In addition, we have used lower therapeutic doses compared with those that have been reported.^{16,20} However, several other reviews of the literature have demonstrated a potential association with the complications. In addition, the recent randomized controlled trial by Gill and colleagues²¹ demonstrated a nonsignificant doubling of serious adverse events and mortality in patients randomly assigned to receive rFVIIa for the management of excessive postoperative bleeding after cardiac surgery. Several recombinant and purified coagulation products are being studied, and those such as rFVIIa may provide clinicians specific agents to treat targeted deficiencies; however, safety is still the most important debate of these therapies.¹²

In this study, patients receiving intraoperative rFVIIa had significantly lower rates of re-exploration for bleeding when compared with a propensity-matched control group of patients (17% vs 48%, $P = .004$). In addition, patients receiving rFVIIa had significantly lower amounts of chest tube output, PRBC, and FFP transfusions. It is possible that the early intraoperative administration of rFVIIa allows it to exert its effects before the onset of such events and potentially reduces the dose required for successful management of coagulopathic bleeding. Some experimental²² and clinical⁷ studies have shown that hypothermia and acidosis may have a negative impact on the efficacy of rFVIIa. Several factors, including hemorrhage and transfusion of blood and blood products, are major contributors to the development of postoperative hypothermia and acidosis. Further experimental studies and larger clinical cohorts are needed to verify the potential benefit of earlier

TABLE 4. Total thrombosis-related events (n)

	rFVIIa n = 29	Control n = 29	Total n = 58
Stroke	1	2	3
TIA	1	1	2
MI	0	1	1
Venous thrombosis	0	0	0
PE	0	0	0
Arterial thrombosis	0	0	0
Total	2	4	6

TIA, Transient ischemic attack; MI, myocardial infarction; PE, pulmonary embolism; rFVIIa, recombinant activated factor VII.

administration of low-dose rFVIIa. However, a trend for increased mortality was observed in both low- and medium-dosing schedules of rFVIIa when this agent was used as a first-line therapy in a recent randomized controlled trial.²¹

The incidence of prolonged intubation in the rFVIIa group was lower than that in the control group. It is a well-known fact that excessive bleeding after open surgery is an important factor that can prevent early extubation.²³ The lower incidence of prolonged intubation in the rFVIIa group may also be due to fewer PRBC and FFP transfusions and the decreased incidence of surgical re-exploration due to mediastinal bleeding in the rFVIIa group. However, intraoperative rFVIIa treatment did not affect the median ICU stay, hospital stay, and in-hospital mortality.

The safety of rFVIIa has been controversial owing to its reported risk of increased thrombotic complications.²⁴ Several reports suggest that a range of 45 to 90 $\mu\text{g}/\text{kg}$ might be safe and effective when administered postoperatively.²⁵ With our low-dose regimen, we had only 2 patients (7%) with potential thrombosis-related events. A multinational registry of rFVIIa use in patients undergoing cardiac surgery suggests a 4% thromboembolic event rate and a 7% possible or probable adverse event rate at a dose of 92 $\mu\text{g}/\text{kg}$ related to the use of rFVIIa.⁷ This study included 37% of aortic cases in which 9% were related to the aortic arch. In our study, 62% of operations involved the aortic arch and 77% of patients underwent operations with DHCA, facts that demonstrate the increased complexity of the operations. Indeed, we found no significant difference between the rates of thrombotic complications between groups. In this study, mortality was not related to thrombotic complications. The safety of our lower dose may be attributed to the earlier administration of rFVIIa and second tier than previously reported.²¹

Study Limitations

Our study is limited by several factors. This is a retrospective study and is therefore associated with the known biases of such studies. Furthermore, there was a significant difference in baseline prematch variables, thereby mandating the performance of a propensity-matched analysis as outlined previously. This method of propensity match itself was limited by the small number of patients included in the statistical analysis who received rFVIIa. The findings of this study cannot be applied to cases involving coronary revascularization because of the possible detrimental thrombosis-related complications of the small size of coronary arteries. Last, although there was no safety signal detected, this study has inadequate power to detect a difference in serious adverse events or complications. We strongly advocate that future prospective randomized trials be conducted to verify our findings.

CONCLUSIONS

This study shows that the intraoperative low dose of rFVIIa is effective in reducing re-exploration for bleeding, decreasing the need for PRBC and FFP transfusions, and reducing the chest tube output. On the basis of the preliminary results, we recommend that clinicians consider the intraoperative use of low doses of rFVIIa in aortic surgery for managing inadequate hemostasis that is unresponsive to routine hemostatic therapy (eg, platelets, FFP, cryoprecipitate). Further prospective randomized studies and larger cohorts are needed to verify these findings.

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