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Recombinant Activated Factor VII for Postoperative Hemorrhage Following Repair of Acute Type A Aortic Dissection

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ABSTRACT

Background: Perioperative hemorrhage in the repair of acute type A aortic dissection increases morbidity, mortality, and costs of treatment. Recombinant activated factor VII (rFVIIa) mitigates intractable blood loss in surgery. By enhancing thrombin generation on activated platelet surfaces and activating thrombin-activatable fibrinolysis inhibitor and factor XIII, rFVIIa promotes platelet aggregation and fibrin plug formation at the site of endothelial injury. We report outcomes for type A aortic dissection patients treated postoperatively with rFVIIa for life-threatening hemorrhage.

Methods: Patients charts were reviewed to gather demographic, procedural, and laboratory data as well as information regarding clinical outcomes and blood product use.

Results: Nine patients with acute type A aortic dissection received rFVIIa in the perioperative period. In the 6 hour period after rFVIIa treatment, transfusion of blood products was reduced. The international normalized ratio decreased after treatment (1.6 versus 0.9, $P < .01$). One patient experienced perioperative stroke.

Conclusions: In patients with acute type A aortic dissections who have life-threatening bleeding, early administration of rFVIIa may safely normalize coagulation variables, decrease transfusion requirements, and enhance hemostasis.

INTRODUCTION

Acute type A aortic dissection is an emergent disease associated with high mortality [Hagan 2000]. Perioperative hemorrhage contributes to morbidity and mortality and increases the costs of treating this disease. Patients often require multiple transfusions of blood products and surgical re-exploration for bleeding, both of which are risk factors for morbidity and mortality [Moore 1997]. Recombinant activated factor VII (rFVIIa) enhances thrombin generation on activated platelet surfaces and activates thrombin-activatable fibrinolysis inhibitor and factor XIII, thereby promoting platelet aggregation and fibrin plug formation at the site of endothelial injury [Hedner 2006].

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rFVIIa has been used to treat intractable blood loss. It was initially developed to treat patients with hemophilia A or B with inhibitors to factors VIII or IX [Shapiro 1998] and has been shown to be safe and effective in this population [Abshire 2004]. rFVIIa has also been used for cases of life-threatening hemorrhage in non-hemophiliac patients where conventional therapy was not sufficient for homeostasis, demonstrating benefit in different surgical fields including trauma [Dutton 2004], urology [Friederich 2003], neurosurgery [Mayer 2005], and cardiac surgery [Karkouti 2005; Romagnoli 2006].

Recent studies in cardiac surgery consist primarily of case reports or series and retrospective chart reviews. Several comparative studies have also been published indicating benefits in adult patients including reduced transfusion requirements, blood loss, international normalized ratio (INR), and intensive care unit (ICU) stay [Diprose 2005]. Although evidence seems to indicate a potential role for rFVIIa in treatment for intractable bleeding in cardiac surgery, safety has been a primary concern, particularly with regards to thromboembolic complications. A recent systematic review of the evidence on rFVIIa use in cardiac surgery found the rate of thromboembolic adverse events to be 5.3% in adults [Warren 2007].

Although several studies of rFVIIa use for life-threatening hemorrhage in cardiac surgery have included aortic dissections in their patient populations [Hyllner 2005; Raivio 2005; Bishop 2006; Filsoufi 2006], no studies have assessed outcomes specifically for rFVIIa use specifically in this disease process. Herein we report outcomes for acute type A aortic dissection patients treated with early administration of rFVIIa for life-threatening hemorrhage.

MATERIALS AND METHODS

Approval of the study protocol was granted by the University of Alberta Health Research Ethics Board. Of all 87 cardiac surgery patients who received rFVIIa, we retrospectively reviewed all 9 patients who received rFVIIa in the perioperative period for surgical repair of acute type A aortic dissection.

All patients had intractable blood loss either during or immediately after surgical repair of an acute type A aortic dissection that required significant transfusion. Conduct of the operation was at the surgeons' discretion. After completion of cardiopulmonary bypass and full reversal of heparin, thorough inspection of the surgical field was undertaken. If significant bleeding persisted and no surgically correctable

source of bleeding could be identified, the coagulation disturbance was investigated by standard laboratory examination, and at least 1 attempt was made to correct the coagulopathy with blood products (fresh frozen plasma [FFP], platelets, and cryoprecipitate). Should the surgeon then deem chest closure inappropriate because of persistent bleeding, consideration for administration of rFVIIa was made and consultation with a hematologist experienced in the use of rFVIIa was sought. Based on the clinical scenario including an assessment of contraindications to rFVIIa, a joint decision to release rFVIIa was made. Aprotinin was administered intraoperatively in all cases.

Transfusion of packed red blood cells, platelets, FFP, and cryoprecipitate intraoperatively and up to 12 hours post-rFVIIa treatment was noted. Clinical outcomes were documented as postoperative chest tube blood losses over 24 hours, length of stay in ICU, thromboembolic complications, other major complications, and deaths.

Continuous variables were compared by the paired-sample t test using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). A *P* value of less than .05 was considered statistically significant.

RESULTS

Nine patients with type A aortic dissection received rFVIIa due to perioperative hemorrhage. Demographic data are presented in Table 1. The mean patient age was 69.7 years (range, 44-78 years) and 4 patients (44%) were female. All patients presented with an acute type A aortic dissection except for 1 patient who was hospitalized for severe back pain and GI bleeding prior to her diagnosis of acute type A aortic dissection. One patient underwent postoperative mediastinal exploration for continued bleeding following administration of rFVIIa. The right musculophrenic branch of the epigastric artery was identified and ligated. Seven patients were treated with rFVIIa in the operating room, and 2 patients received rFVIIa postoperatively in the ICU. Further operative details are presented in Table 1.

Prior to administration of rFVIIa the patients received transfusions of, on average, 4.7 units of FFP, 9.0 units of platelets, 5.0 units of cryoprecipitate, and 5.7 units of packed red blood cells (Table 2). In the 6-hour period following administration of rFVIIa, the requirement for blood products was decreased, with patients receiving an average of 1.3 units of FFP ($P = .037$), 2.3 units of platelets ($P < .01$), 2.4 units of cryoprecipitate (P = ns), and 1.9 units of packed red blood cells (P = ns). Three patients (33%) received no further blood products after rFVIIa was given.

Coagulation parameters measured within 4 hours before and after rFVIIa treatment indicate a change toward normalization of the INR and partial thromboplastin time (PTT). INR normalized from 1.6 before treatment to 0.9 after treatment ($P < .01$) (Table 3). The reduction in PTT was notable but did not reach statistical significance. Platelet, hemoglobin, and hematocrit levels did not change significantly.

Chest tube drainage in the first 6 hours following administration of rFVIIa was 57 mL/hour and decreased to 19 mL/hour in the following 6 hours.

Patients were hospitalized in the ICU for a mean of 13.3 days (range, 5-28 days) after surgical repair of their aortic dissections. There was a single in-hospital mortality.

Table 1. Patient Demographics*

Patient Number	Age, y/Sex	EF†	HTN	Hyperlipidemia	COPD	PND	RF	Other Comorbidities	Re-Operation	CPB time, min	Cross-Clamp Time, min	Circulatory Arrest Time, min	Surgical Re-Exploration	rFVIIa given OR/ICU	Dose rFVIIa, mg
1	73/F	N	—	—	yes	yes	yes	—	no	146	83	24	no	OR	4.8
2	78/f	60	yes	—	—	—	—	—	no	142	103	25	no	ICU	4.8
3	78/F	N	yes	—	—	—	—	tamponade	no	173	93	36	no	OR	4.8
4	64/M	N	yes	yes	—	—	—	Raynauds disease, CAD	no	263	63	36	no	OR	4.8
5	69/M	50-55	—	yes	yes	yes	yes	PAD	yes	352	245	70	no	OR	NA
6	68/F	—	—	—	—	—	—	aortic root aneurysm	no	299	239	37	no	OR	3.6
7	78/M	40-45	yes	—	—	—	—	CHF tamponade	no	151	83	24	no	OR	4.8
8	75/M	—	yes	—	—	—	—	—	no	171	102	NA	yes	ICU	8.4
9	44/M	N	—	—	—	—	—	—	no	183	102	0	no	OR	4.8

*EF indicates left ventricular ejection fraction; HTN, hypertension; COPD, chronic obstructive pulmonary disease; PND, preoperative neurological deficit; RF, renal failure; CPB, cardiopulmonary bypass; OR, operating room; ICU, intensive care unit; rFVIIa, recombinant activated factor VII; CAD, coronary artery disease; PAD, peripheral artery disease; CHF, congestive heart failure.

†N indicates left ventricular function estimated to be normal on echocardiogram.

Table 2. Blood Products Consumed Before and After Recombinant Activated Factor VII (rFVIIa)

Blood Products	Pre-rFVIIa (n = 9), mean (range)	0 to 6 Hours Post-rFVIIA (n = 9), mean, range	*P*
Plasma, units	4.7 (2-8)	1.3 (0-6)	.037
Platelets, units	9.0 (5-12)	2.3 (0-6)	.001
Cryoprecipitate, units	5.0 (0-10)	2.4 (0-10)	.233
Red blood cells, units	5.7 (1-15)	1.9 (0-6)	.053

Table 3. Coagulation Profile Before and After Recombinant Activated Factor VII (rFVIIa)*

Coagulation Profile	Normal Range	Pre-rFVIIA, mean (range)	Post-rFVIIA, mean (range)	*P*
INR	0.8-1.2	1.6 (0.8-2.3)	0.9 (0.8-1.2)	.001
PTT, s	24-35	84.6 (43->200)	47.8 (33-78)	.111
Fibrinogen, g/L	2.3-4.5	2.2 (1.1-3.7)	—	—
Platelets, $\times 10^9$/L	140-450	115.4 (70-145)	129.6 (72-158)	.343
Hemoglobin	120-160	90.3 (81-107)	94.9 (63-119)	.388
Hematocrit	36-46	28.3 (25-34)	27.8 (20-35)	.804

*INR indicates international normalized ratio; PTT, partial thromboplastin time.

Table 4. Clinical Outcomes*

Patient Number	ICU Stay, d	Death	Cause of Death	Major Complications
1	NA	yes	cardiac arrest	renal failure
2	5	no	—	urinary tract infection
3	25	no	—	stroke, prolonged intubation
4	7	no	—	—
5	10	no	—	atrial fibrillation
6	18	no	—	paraplegia
7	7	no	—	renal failure, respiratory failure
8	28	no	—	sepsis, pneumonia
9	6	no	—	atrial fibrillation

*ICU indicates intensive care unit. Patient number 6 presented with paraplegia that did not resolve following repair.

Patient 1 suffered a fatal asystolic cardiac arrest. One patient (11%) experienced a perioperative cerebral vascular accident. Patient 3 suffered a left hemispheric infarct resulting in right-sided paralysis. After 2 months, the patient recovered sufficient right-sided movement to walk and was discharged to a stroke rehabilitation unit. Other major medical complications are reported in Table 4.

DISCUSSION

Although other authors report administering rFVIIa only after an exhaustive attempt to reduce bleeding and correct coagulopathy, we were more aggressive in treating postoperative hemorrhage with rFVIIa. Early treatment in hemophilia has reduced morbidity and blood product usage [Lusher 1998] and may also provide additional benefits in surgical hemorrhage.

Surgical bleeding frequently necessitates transfusion of allogeneic red blood cells and other blood components, which is a risk factor for re-operation. Allogeneic red blood cell transfusion is associated with an 8-fold increase in the risk of mortality and decreased long-term survival [Gill 2009]. Therefore, early rFVIIa administration may reduce overall blood product usage and associated morbidity and mortality. Earlier and even prophylactic use of rFVIIa is supported by a small trial that randomized patients to either rFVIIa or placebo following administration of protamine at the completion of cardiopulmonary bypass. Patients receiving rFVIIa benefitted by receiving significantly fewer blood products than the treatment arm compared to the placebo arm while maintaining a similar risk profile [Diprose 2005].

Prolonged hemorrhage and massive component blood transfusion are associated with hypotension, use of vasopressors, cardiac tamponade, and the lethal cascade of

hypothermia, acidosis, and worsening coagulopathy resulting in multi-organ system failure. In addition, rFVIIa is less effective in the setting of acidosis. Failure of some trials of rFVIIa may be from treatment beyond the "Golden Hour" of resuscitation. Early intervention with rFVIIa may prevent physiological derangement associated with massive hemorrhage and resuscitation thereby avoiding multi-organ system failure [Aitken 2004].

Despite its high cost, early treatment with rFVIIa may reduce the overall cost of treating refractory surgical coagulopathy. In the United States, the cost of rFVIIa is $1100 per 1-mg vial. Therefore, the average cost per patient treated in our study was $5600. At our hospital, the cost of transfusion of a unit of packed red blood cells is $235, platelets $500 per pack, FFP $55 per unit, and cryoprecipitate $340 per 6-pack; however, these costs are likely underestimated because direct and indirect overhead costs associated with transfusion of 1 unit of packed red blood cells are between $522 and $1183 [Shander 2010]. Early intervention with rFVIIa was shown to be most cost effective early in the transfusion period [Loudon 2005].

A recent randomized trial in patients undergoing coronary artery bypass grafting and valve surgery failed to detect a significant difference in thrombotic complications, but patients receiving rFVIIa required fewer re-operations for bleeding and less transfusion of blood products [Gill 2009]. We examined clinical outcomes for 9 patients undergoing surgical repair of acute type A aortic dissection who received rFVIIa for severe perioperative bleeding. Following treatment with rFVIIa there was a reduction in blood loss, an improvement in the coagulation profile, and patients required few additional blood products.

Although, to our knowledge, no other studies have examined rFVIIa use exclusively in aortic dissection repair patients, several studies of cardiac surgery patients have included aortic dissections. Bishop et al [2006] reviewed rFVIIa use in 12 cardiac patients, 5 of whom were acute aortic dissection repair. They also found a significant decrease in INR and a downward trend in PTT. They observed a highly statistically significant decrease in blood product consumption. Filsoufi et al [2006] found similar results when they examined 17 cardiac surgery patients. Seven of these were aortic operations, 4 being type A dissections. These investigators found significant decreases in coagulation variables and the need for transfusions after rFVIIa treatment. Bishop et al [2006] and Filsoufi et al [2006] observed no thromboembolic complications in their study samples.

Raivio et al [2005] similarly found significantly decreased blood product use in their study of 16 cardiac surgery patients given rFVIIa. Four of these were acute type A aortic dissections. They did, however, observe a high frequency of thromboembolic or thrombotic complications. In total they recorded 4 patients (25%) who suffered from a thromboembolic complications, 2 of whom were acute type A aortic dissection repairs. One suffered left-sided paralysis, and a computed tomography scan identified "multiple embolic infarcts bilaterally." Their other patient experienced thrombosis of the right iliac artery. This study was found to have the " . . . highest thromboembolic adverse event rate in those receiving rFVIIa . . . " in a recent systematic review by Warren and collegues [2007] .

rFVIIa has been studied as a treatment for intractable blood loss in surgical patients. By acting on activated platelet surfaces, rFVIIa can focus its activity on sites of vascular injury, thereby minimizing perioperative hemorrhage; however, neutrophils and monocytes stimulated by inflammatory cytokines may express tissue factor and therefore may interact with rFVIIa in the blood leading to procoagulant effects in other sites besides vascular injury [Maugeri 2006]. Consequently, because inflammatory cytokines are up-regulated and neutrophils are activated during cardiopulmonary bypass, there is concern that administration of rFVIIa following cardiac surgery may lead to deleterious arterial and microvascular thrombosis.

We observed a thromboembolic complication rate of 11%, which may be influenced by the emergent nature of the acute type A aortic dissection repair. The patient who suffered a stroke was at higher risk for a neurological event, being of advanced age and hypertensive. This patient also suffered preoperative cardiac tamponade as a result of the aortic dissection, with large amounts of blood and clot identified in the pericardium during repair.

We have found that rFVIIa can be used in patients with acute type A aortic dissections who have life-threatening bleeding to normalize coagulation variables, decrease transfusion requirements, and help attain hemostasis. The risk of thromboembolic complications may be increased in this patient population, however. This risk may still be outweighed by the risk of mortality due to severe bleeding and the risks associated with allogeneic red blood cell transfusion. Randomized controlled trials would further evaluate the risk-benefit ratio in this patient population.

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