Determinants of complications with recombinant factor VIIa for refractory blood loss in cardiac surgery

[Les déterminants de complications avec le facteur VIIa recombinant utilisé pour les pertes sanguines réfractaires en chirurgie cardiaque]

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Purpose: Recombinant factor VIIa (rFVIIa) is being used for refractory, excessive blood loss (EBL) after cardiac surgery, but its safety for this indication is not known.

Methods: The unadjusted and risk-adjusted adverse event (AE) rates were compared between 114 consecutive cardiac surgical patients who received rFVIIa for refractory EBL and 541 concurrent patients who developed EBL but did not receive rFVIIa. Similarly, timing of rFVIIa therapy was assessed by dichotomizing rFVIIa patients based on median number of red blood cell (RBC) units received before therapy. The measured AE was a composite of death, stroke, renal failure, myocardial infarction, and major vein thrombosis. For risk adjustment, logistic regression models for this outcome were constructed using known predictors of AEs.

Results: The median RBC units transfused before rFVIIa therapy was eight. The AE rates in the untreated, early (≤ 8 U), and late (> 8 U) treated patients were 24% (129/541), 30% (20/66), and 60% (29/48). The risk-adjustment model included total RBC units, pump time, weaning difficulty, gender, weight, and age. The unadjusted and adjusted AE odds ratios (OR) in the treated vs untreated groups were 2.41 [confidence interval (CI) 1.58 – 3.67; $P < 0.0001$] and 1.04 (CI 0.60 – 1.81; $P = 0.9$). In the rFVIIa group, the adjusted AE OR was lower in the early treated group (OR 0.41; CI 0.18 – 0.92; $P = 0.03$).

Conclusion: In cardiac surgical patients with refractory hemorrhage, rFVIIa therapy is not associated with increased risk of AEs, and early treatment may be associated with better outcomes.

Objectif : Le facteur VIIa recombinant (rFVIIa) est utilisé pour traiter les pertes sanguines excessives (PSE) réfractaires après une opération cardiaque sans qu'on en connaisse l'innocuité.

Méthode : Les taux d'événements indésirables (EI) non ajustés et ajustés en fonction des risques ont été comparés entre 114 patients consécutifs de cardiologie ayant reçu le rFVIIa pour des PSE et 541 patients consécutifs qui ont eu des PSE mais pas de rFVIIa. De même, la programmation du traitement au rFVIIa a été étudiée par une division dichotomique des patients, recevant le rFVIIa, fondée sur le nombre médian d'unités de culots globulaires (CG) reçues avant le traitement. Les EI étaient la mort, l'accident vasculaire, l'insuffisance rénale, l'infarctus du myocarde et la thrombose veineuse majeure. Des modèles de régression logistique ont été construits pour ajuster le risque en utilisant les prédictors connus d'EI.

Résultats : La médiane des unités de CG transfusées avant le traitement au rFVIIa a été de huit. Les taux d'EI chez les patients non traités, traités tôt (≤ 8 U) et tard (> 8 U) ont été de 24 % (129/541), 30 % (20/66) et 60 % (29/48). Le modèle d'ajustement du risque comprenait le nombre total d'unités de CG, le temps de perfusion, les difficultés de sevrage, le sexe, le poids et l'âge. Les risques relatifs (RR) d'EI non ajustés et ajustés chez les patients traités vs non traités ont été de 2,41 [intervalle de confiance (IC) de 1,58 – 3,67 ; $P < 0,0001$] et 1,04 (IC 0,60 – 1,81 ; $P = 0,9$). Dans le groupe rFVIIa, le RR d'EI ajusté a été plus bas chez les patients traités tôt (RR 0,41 ; IC 0,18 – 0,92 ; $P = 0,03$).

Conclusion : Chez les patients de cardiologie victimes d'hémorragie réfractaire, le traitement au rFVIIa n'est pas associé

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à un risque accru d'EI et le traitement précoce peut être associé à de meilleurs résultats.

BLOOD loss that becomes refractory to standard hemostatic interventions is a serious complication of cardiac surgery that is associated with significant morbidity and mortality.¹⁻⁴ Recombinant factor VIIa (rFVIIa), a hemostatic agent currently approved for hemophiliac patients with antibodies against specific coagulation factors, is now being used for refractory blood loss after cardiac surgery in the absence of any randomized controlled trials of its safety or efficacy for this indication. This “off-label” use is primarily based on several case series and case-control studies that indicate rFVIIa is highly effective in reducing or stopping refractory bleeding after cardiac surgery.⁵ The high rate of serious adverse events in these reports, however, has raised concerns about the safety of rFVIIa in cardiac surgery.

A particularly important safety concern is the potential for thrombotic complications. Following cardiac surgery with cardiopulmonary bypass (CPB), there is up-regulation of tissue factor (TF) expression both locally in areas of tissue injury and systemically.^{6,7} Given that the mechanism of action of rFVIIa in part involves binding to TF,⁸ increased TF expression may lead to more systemic clot formation.⁹ This is of particular concern in patients with excessive blood loss, in whom organ hypoperfusion and reperfusion injury resulting from inadequate or delayed resuscitation may lead to disseminated intravascular coagulation,¹⁰ which increases systemic TF expression,¹¹ and may therefore increase the risk of thrombotic complications with rFVIIa therapy.

Furthermore, rFVIIa therapy may increase the incidence of acute coronary events in patients undergoing coronary artery bypass grafting or in those who have vulnerable atherosclerotic plaques in their coronary vasculature.⁹ It has also been postulated that rFVIIa may contribute to multi-organ failure by modulating the inflammatory response in the setting of systemic inflammatory response syndrome,^{12,13} which commonly occurs after cardiac surgery with CPB.¹⁴ In addition, antifibrinolytic drugs that are frequently used to preserve the hemostatic system during CPB may further increase the risk of thrombotic complications with rFVIIa.⁵

Although adequately powered randomized controlled clinical trials are required to definitively assess the safety of rFVIIa in cardiac surgery, to date none is available. Consequently, we carried out this obser-

vational study to identify the determinants of complications associated with rFVIIa therapy in a cohort of cardiac surgical patients with excessive blood loss, some of whom, owing to the refractory nature of their blood loss, received rFVIIa.

Methods

Study setting and clinical practice

The Toronto General Hospital is a teaching hospital affiliated with the University of Toronto. A full range of adult cardiac surgery procedures were performed by 13 surgeons during the study period (November 2002 to April 2005). Patient management during this period has been previously described.^{15,16}

In November 2002, a clinical protocol for the off-label use of rFVIIa (NiaStase®, Novo Nordisk, Mississauga, ON, Canada) in patients with excessive, refractory hemorrhage after cardiac surgery was introduced at our institution, the details of which have been previously described.⁴ The protocol for management of bleeding cardiac surgical patients is shown in the Figure. According to the protocol, patients were eligible for rFVIIa if they had 1) > 2,000 mL of blood loss or received $\geq$ four units of red blood cell concentrate (RBC); 2) ongoing blood loss that precluded sternal closure in the operating room or was ongoing at > 100 mL·hr⁻¹ in the intensive care unit; and 3) blood loss that was refractory to conventional treatment. Blood loss was considered to be refractory if all of the following criteria were met: 1) a surgical source of bleeding was excluded by at least two hours of surgical exploration after termination of CPB and reversal of heparin or by returning to the operating room for re-exploration; 2) antifibrinolytics (tranexamic acid 100 mg·kg⁻¹ or more, or aprotinin 6×10^6 IU or more) were administered; 3) at least the equivalent of five units of random donor platelets and four units of fresh frozen plasma were administered; 4) and attempts were made to correct coagulation parameters and to achieve target hematocrit and platelet counts (Figure).

Patients were initially identified by attending surgeons, anesthesiologists, or intensive care physicians, and subsequently referred to a hematologist who made the final determination as to whether the patient was eligible for rFVIIa therapy. This determination was based on the perceived risks of ongoing blood loss vs the potential risks of rFVIIa and the criteria listed in the protocol. The initial recommended dose of rFVIIa was 2.4 to 4.8 mg based on the severity of bleeding as judged by the clinical team. A second dose of rFVIIa (2.4–4.8 mg) was permitted after 30 to 60 min if there was continued excessive blood loss (rate > 100 mL·hr⁻¹).

FIGURE Protocol for management of bleeding cardiac surgery patients. *Evidence of microvascular bleeding postreversal of heparin in the operating room or > 100 mL·hr⁻¹ drainage from mediastinal tubes in the ICU; †Antifibrinolytic top-up: if early bleed and aprotinin used, continue at 50,000 KIU·hr⁻¹; if tranexamic acid used or late bleed, consider tranexamic acid bolus 50 mg·kg⁻¹. Protamine: target activated clotting time (ACT) within 10% of baseline or until there is no response to additional protamine administration; ‡May give 5 U RDP if at risk for qualitative platelet disorder (deep hypothermic circulatory arrest (DHCA); prolonged CPB; recent anti-platelet therapy) irrespective of platelet counts; POC = point-of-care; blwk = blood work; ABG = arterial blood gases; Hct = hematocrit; lytes = electrolytes; Ca = ionized calcium; CBC = complete blood count including hemoglobin concentration and platelet count (Plt); Coags = coagulation profile including prothrombin time, partial thromboplastin time, international normalized ratio (INR), and fibrinogen (Fib); OR = operating room; ICU = intensive care unit; RBC = red blood cell concentrate; RDP = random donor platelet; FFP = fresh frozen plasma; Cryo = cryoprecipitate; rFVIIa = recombinant activated factor VII.

Data sources, study population, and primary outcome

Following Institutional Ethics Board approval, study data were retrieved from patients' medical records and prospectively collected, validated databases that have been described previously.^{4,15} The data included

patient characteristics, intraoperative course, and post-operative outcomes. Full-time research personnel blinded to the nature of this study prospectively adjudicated all outcomes from patients' medical records.

For the purposes of this study, any patient who underwent cardiac surgery with CPB and received at least four units of RBC within one day of surgery and who needed both fresh frozen plasma and platelet transfusions was considered to have had excessive blood loss and was included in the study cohort.

The primary outcome was the composite of the following in-hospital adverse events: stroke (any persistent new postoperative neurological deficit); acute renal failure (new requirement for dialysis support or a greater than twofold increase from baseline creatinine to highest postoperative creatinine within one week of surgery); myocardial infarction (new Q wave on postoperative electrocardiogram or new electrocardiogram changes accompanied by MB isoenzyme of creatine kinase $> 50 \text{ U}\cdot\text{L}^{-1}$ with the CK-MB/CK ratio $> 5\%$ or troponin I $> 10 \text{ }\mu\text{g}\cdot\text{L}^{-1}$); major vein thrombosis (radiological or autopsy evidence); and death.

Statistical analysis

Baseline characteristics and outcomes of the study cohort who did and did not receive rFVIIa were compared using the Chi-square or Fisher's exact tests for categorical variables and the t test or Wilcoxon rank-sum test for continuous variables.

The number of units of RBC transfused within one day of surgery was obtained in all patients. For patients who received rFVIIa, the number of RBC units initiated before and after the first dose of rFVIIa was also obtained. Patients at or below the median number of units were classified as the "early therapy" group, and those above the median were classified as the "late therapy" group.

Logistic regression modelling was used to determine the unadjusted and adjusted adverse event odds ratios (OR) associated with rFVIIa therapy and timing of rFVIIa therapy. To calculate the unadjusted OR for rFVIIa therapy, a model was constructed with rFVIIa therapy as the sole covariate, analyzed as three independent binomial variables: none, early, and late therapy.

To calculate the risk-adjusted OR for rFVIIa therapy, the entire cohort was used and all perioperative variables associated ($P < 0.1$) with the composite adverse event in bivariate analysis were included in the modelling. To assess the role of timing of rFVIIa therapy, another model was constructed using only the rFVIIa treated patients. In this model, rFVIIa was analyzed as a binomial variable based on timing of therapy, and no adjustment was made for RBC units transfused. The multivariable models were constructed using backward stepwise variable selection and a P -value of ≤ 0.05 was used as the criterion for

TABLE I Patient characteristics

Variable	No rFVIIa group (<i>n</i> = 541)	rFVIIa group (<i>n</i> = 114)	<i>P</i> -value
Preoperative patient characteristics			
Age (yr)	65 $\pm$ 13	59 $\pm$ 17	0.001
Weight (kg)	73 $\pm$ 16	71 $\pm$ 16	0.3
Female	207 (38%)	32 (28%)	0.04
Diabetes (type I or II)	127 (23%)	23 (20%)	0.4
Hypertension	313 (58%)	49 (47%)	0.03
Left ventricular dysfunction	144 (27%)	34 (30%)	0.5
Peripheral vascular disease	108 (20%)	23 (20%)	0.9
Cerebrovascular disease	76 (14%)	8 (8%)	0.08
Atrial fibrillation	66 (12%)	14 (12%)	0.9
Congestive heart failure	238 (44%)	52 (46%)	0.7
Active endocarditis	21 (4%)	7 (6%)	0.3
Preoperative renal dysfunction	157 (29%)	36 (32%)	0.6
Preoperative hemoglobin ($\text{g}\cdot\text{L}^{-1}$)	123 $\pm$ 18	127 $\pm$ 22	0.05
Surgical variables			
Urgent surgery	92 (17%)	30 (26%)	0.02
Redo surgery	110 (20%)	35 (31%)	0.01
Complex surgery	328 (61%)	90 (79%)	0.0002
Received aprotinin	136 (25%)	54 (50%)	< 0.0001
CPB duration (min)	140 $\pm$ 59	166 $\pm$ 71	0.0002
Deep hypothermic circulatory arrest	52 (10%)	22 (19%)	0.003
Difficult wean from CPB	203 (38%)	59 (52%)	0.005
Re-exploration	165 (31%)	76 (67%)	< 0.0001

rFVIIa = recombinant factor VIIa; CPB = cardiopulmonary bypass; left ventricular dysfunction = ejection fraction $< 40\%$; preoperative renal dysfunction = creatinine ($\mu\text{mol}\cdot\text{L}^{-1}$) > 100 in women, > 110 in men, or on dialysis; complex surgery = any procedure except isolated coronary artery bypass grafting or single valve surgery; received aprotinin = all others received tranexamic acid; difficult wean from CPB = requirement for two or more inotropes or intra-aortic balloon pump upon termination of CPB.

variable retention. Potentially important confounders that did not meet the 0.05 thresholds were forced into the primary model. In addition, rFVIIa therapy was forced into both models if its P -value was > 0.05 . The Hosmer-Lemeshow test was used to test the calibration and the c-index was used to test the discrimination of the models.¹⁷

Results

Of the 4,630 patients who underwent cardiac surgery with CPB at our institution during the study period, 655 patients (14%) met the criteria for inclusion in the study. Of those, 114 (17%) received at least one dose of rFVIIa for refractory hemorrhage (we have previously reported on the first 51 of these patients focusing on effectiveness of rFVIIa).⁴ Patients who received rFVIIa had undergone a variety of procedures includ-

TABLE II Patient outcomes

Variable	No rFVIIa group (n = 541)	Early rFVIIa group* (n = 66)	Late rFVIIa group* (n = 48)	P-value†
<i>Blood product units transfused from surgery to discharge (median, interquartile range)</i>				
RBC	6 (5, 9)	10 (8, 13)	18 (14, 24)	< 0.0001
Platelets	5 (5, 10)	10 (10, 15)	20 (15, 25)	< 0.0001
FFP	6 (4, 9)	8 (6, 14)	14 (8, 19)	< 0.0001
Total products	19 (14, 28)	30 (23, 41)	46 (34, 65)	< 0.0001
<i>Blood product units transfused before rFVIIa therapy (median, interquartile range)</i>				
RBC	NA	6 (4, 7)	12 (10, 13)	
Platelets	NA	10 (5, 15)	10 (5, 10)	
FFP	NA	8 (4, 8)	16 (4, 25)	
Total products	NA	25 (20, 31)	36 (29, 44)	
<i>Recovery times (median, interquartile range)</i>				
Intubation (hr)	18 (10, 42)	35 (18, 84)	94 (40, 387)	< 0.0001
ICU stay (days)	3 (2, 5)	4 (2, 7)	7 (4, 21)	< 0.0001
Hospital stay (days)	9 (7, 13)	12 (7, 21)	15 (9, 31)	< 0.0001
<i>Adverse outcomes‡</i>				
Death	42 (7.8%)	5 (7.6%)	13 (27.1%)	0.007
Stroke	24 (4.4%)	4 (6.1%)	7 (14.6%)	0.02
Myocardial infarction	25 (4.6%)	2 (3.0%)	6 (12.5%)	0.3
Acute renal failure	81 (15.0%)	13 (19.7%)	20 (41.7%)	0.0003
Pulmonary embolism/ deep vein thrombosis	3 (0.6%)	3 (4.6%)	1 (2.1%)	0.02
Composite adverse event	129 (23.8%)	20 (30.0%)	29 (60.4%)	< 0.0001

rFVIIa = recombinant factor VIIa; RBC = red blood cell; FFP = fresh frozen plasma; ICU = intensive care unit; NA = not applicable;

*Early treatment if $\leq$ eight units RBC before treatment; late treatment if $>$ eight units RBC before treatment. †Comparisons between no-rFVIIa vs any rFVIIa; ‡See text for definitions. All continuous variables are presented as mean $\pm$ SD unless otherwise stated. All categorical variables are presented as n (%).

ing, either singly or in combination, coronary artery bypass grafting surgery ($n = 60$), valve replacement/repair ($n = 63$), ascending aorta or aortic arch replacement/repair ($n = 32$), complex congenital abnormality repair ($n = 14$), heart transplantation ($n = 11$), and insertion of a left ventricular assist device ($n = 4$).

As can be seen in Table I, those in the study cohort who received rFVIIa had a higher overall risk-profile than those who did not receive rFVIIa. Importantly, they more frequently underwent complex surgical procedures requiring longer CPB durations and had a higher incidence of difficult wean from CPB. In the rFVIIa treated group, the median number of RBCs transfused before rFVIIa therapy was eight units (inter-quartile range = 6–11 U). Consequently, patients who received eight or fewer RBC units before rFVIIa therapy were classified as the early therapy group, and those who received more than eight units were classified as the late therapy group. The mean ($\pm$ SD) rFVIIa dose received by rFVIIa treated patients was $56 \pm 25 \mu\text{g}\cdot\text{kg}^{-1}$. It was $54 \pm 22 \mu\text{g}\cdot\text{kg}^{-1}$ in the early-rFVIIa group and $58 \pm 30 \mu\text{g}\cdot\text{kg}^{-1}$ in the late-rFVIIa group ($P = 0.4$). Table II shows the recovery times and adverse events of patients based on treat-

ment with rFVIIa and timing of therapy. As can be seen, compared to untreated patients, rFVIIa patients received substantially more blood products and had slower recovery times and higher adverse event rates. These differences were more pronounced in the late-rFVIIa group.

The composite adverse event rates in the untreated, early and late therapy groups were 24% (129/541), 30% (20/66), and 60% (29/48), respectively. The unadjusted OR for the composite adverse event for the entire rFVIIa group, as well as for early and late rFVIIa groups separately (relative to no rFVIIa) are shown in Table III. As can be seen, rFVIIa therapy was associated with a greater than twofold increase in the odds of the composite adverse event [OR 2.41; 95% confidence interval (CI) 1.58–3.67]. When patients were analyzed according to timing of rFVIIa therapy, only late therapy was associated with increased risk of the composite adverse event.

In multivariable logistic regression modelling in the entire cohort, variables that were considered as potential confounders were age, sex, weight, preoperative hemoglobin, preoperative renal dysfunction, diabetes, cerebral vascular disease, recent myocardial infarction,

TABLE III Adjusted and unadjusted OR and 95% CI for rFVIIa therapy

Comparison	OR	CI	P-value
<i>Entire patient cohort - unadjusted</i>			
All rFVIIa <i>vs</i> no rFVIIa	2.41	1.58–3.67	< 0.0001
Late rFVIIa <i>vs</i> no rFVIIa	4.88	2.64–8.98	< 0.0001
Early rFVIIa <i>vs</i> no rFVIIa	1.39	0.79–2.43	0.3
<i>Entire patient cohort - adjusted</i>			
All rFVIIa <i>vs</i> no rFVIIa	1.04	0.60–1.81	0.9
Late rFVIIa <i>vs</i> no rFVIIa	1.12	0.51–2.49	0.9
Early rFVIIa <i>vs</i> no rFVIIa	0.99	0.51–1.91	0.8
<i>rFVIIa treated patients only - adjusted</i>			
Early rFVIIa <i>vs</i> late rFVIIa	0.41	0.18–0.92	0.03

OD = odds ratios; CI = confidence intervals; rFVIIa = recombinant factor VIIa.

previous sternotomy, type of surgery, CPB duration, deep hypothermic circulatory arrest, type of antifibrinolytic drug used, total RBC units transfused during hospitalization, difficulty weaning from CPB, and treatment with rFVIIa. Variables that were retained in the model were (in order of importance): total RBC units transfused during hospitalization, difficulty weaning from CPB, CPB duration, weight, gender, cerebrovascular disease, and age. The model was reliable (Hosmer-Lemeshow test $P = 0.2$) and discriminative (c-index = 0.78). Since rFVIIa did not remain in the model, it was forced into the model to obtain its adjusted OR for the composite adverse event (Table III). As can be seen, after adjustment for confounders, rFVIIa therapy was not associated with increased adverse event risk (OR 1.04; 95% CI 0.60–1.81).

Constructing the model only in rFVIIa treated patients without adjustment for RBC transfusion, three variables remained in the model – timing of rFVIIa therapy, CPB duration, and history of cerebral vascular disease – all of which were equally predictive (Hosmer-Lemeshow test $P = 0.6$; c-index = 0.71). In this model, the odds for the adverse event were substantially lower in the early *vs* late rFVIIa therapy group (OR 0.41; 95% CI 0.18–0.92), (Table III).

Discussion

Although the definition of excessive blood loss varies from study to study,¹⁸ a consistent finding among studies is that cardiac surgical patients who bleed excessively and require transfusion of multiple blood products are at increased risk for serious adverse events.^{15,18–28} In a previous study, we found that in

about one-fifth of patients with excessive blood loss, or about 2% of the general cardiac surgery population, blood loss becomes refractory to standard hemostatic interventions that include surgical intervention, local and systemic hemostatic agents, and transfusion of blood products.⁴ The consequences of refractory blood loss are particularly severe, resulting in organ failure or death in a large proportion of patients and markedly increasing recovery times and use of health care resources.^{1–4} It is therefore not surprising that the off-label use of rFVIIa for this high-risk patient population has garnered the recommendation of experts in the field of transfusion medicine and clinicians' acceptance (as is indicated by the increasing number of published case series), despite the lack of efficacy data from randomized controlled trials and, in particular, unresolved concerns about its safety in cardiac surgery.^{5,29}

Highlighting this safety concern is the high incidence of serious adverse events in published case series of rFVIIa in cardiac surgery.⁵ Because the majority of studies to date have lacked a control arm, however, it is difficult to ascertain if the adverse events in rFVIIa patients are related to rFVIIa therapy or to patients' underlying medical status. We attempted to answer this question in our previous study by comparing the outcomes of the first 51 cardiac surgery patients who received rFVIIa for refractory excessive hemorrhage at our institution to propensity matched controls identified from our general cardiac surgery population.⁴ We found that while the mortality risk was comparable between the two matched groups, the risks of renal failure and stroke were higher in the rFVIIa group. Owing to that study's limitations, which included a relatively small sample size and the inability to fully match patients for important confounders such as amount of perioperative blood transfusion, however, no definitive conclusions could be drawn about the safety of rFVIIa. The current study included a larger sample size of patients treated with rFVIIa, and to allow for better risk-adjustment, the baseline risk was obtained from patients with excessive blood loss rather than the general cardiac surgery population.

In this study, rFVIIa therapy was strongly associated with the composite adverse event when risk-adjustment was not performed (OR 2.41; 95% CI 1.58–3.67). After risk-adjustment was carried out for important confounders such as RBC transfusions and CPB duration, however, rFVIIa therapy was no longer associated with the composite adverse event (OR 1.04; 95% CI 0.60–1.81). It is important to note that by adjusting for RBC transfusions, any beneficial effects of rFVIIa would have been masked in this anal-

ysis since, in effect, it compares rFVIIa treated patients with untreated patients who had similar amounts of blood loss.

Ideally, randomized placebo-controlled clinical trials should be carried out to detect any beneficial effects of rFVIIa on hemostasis and clinical outcomes. Nevertheless, we carried out an exploratory analysis to determine if rFVIIa therapy early in the course of blood loss was associated with improved outcomes compared with those treated late in the course of blood loss. For this analysis, we classified patients as early or late therapy based on the number of RBC transfusions before the first dose of rFVIIa therapy, and compared the risk-adjusted outcomes of the two groups without adjusting for total RBC transfusions. We found that the risk-adjusted composite adverse event rate was substantially lower in the early treatment group (early *vs* late OR 0.41; 95% CI 0.18–0.92). By not adjusting for RBC transfusions, this analysis assumes that, and is valid only if, all rFVIIa treated patients had refractory hemorrhage. Within the confines of this assumption, our finding suggests that patients with refractory blood loss may benefit from early therapy with rFVIIa. Although this finding needs to be confirmed by future studies, such an association is plausible given that patients with greater blood loss are more likely to develop hemodynamic instability and subsequent disseminated intravascular coagulation,¹⁰ and rFVIIa therapy in the presence of disseminated intravascular coagulation may increase the risk of thrombotic complications.³⁰ Others have also found that rFVIIa therapy, when used as a “last-ditch” intervention in patients who have already lost a large amount of blood, may be ineffective and is associated with very high mortality rates.²

This study has several important limitations. First, since rFVIIa was guided by a clinical protocol rather than a rigid experimental protocol, there was considerable heterogeneity in the subjects’ baseline risk, surgical complexity, condition at time of rFVIIa therapy (e.g., amount and rate of blood loss, hemodynamic status, organ compromise), and dosage and timing (relative to surgery) of rFVIIa therapy. Although a hematologist reviewed all rFVIIa requests to confirm that the criteria for excessive, refractory hemorrhage were met, it is possible that some patients who received early rFVIIa therapy did not have refractory hemorrhage. If this was the case, then it may account for the observed difference in adverse event rates between the early and late rFVIIa therapy groups.

Second, as in any other observational study, the results of this study can only identify associations rather than cause-effect relationships, and may be affected

by unmeasured confounders. This is particularly relevant for the early *vs* late rFVIIa therapy analysis, as the observed risk difference between the two groups may not necessarily be related to the timing of rFVIIa therapy, but may be due to unmeasured confounders.

Another important limitation of this study is its small sample size of patients treated with rFVIIa, which is reflected in the relatively large CI of the measured OR. Consequently, larger observational studies or, ideally, prospective randomized controlled trials are required to confirm or refute the findings of this study.

In conclusion, this study suggests that the association between rFVIIa therapy and postoperative adverse events is due to the effects of confounders, and that rFVIIa therapy may be associated with improved outcomes if it is given early in the course of blood loss. Although the use of rFVIIa in cardiac surgery seems to be increasing, the number of patients requiring rFVIIa therapy for refractory blood loss at any one institution is still sufficiently low that determination of the true predictors of outcomes is difficult. In light of these and other corroborative preliminary evidence,³¹ therefore, definitive randomized multicentre clinical trials are warranted to assess the effects of rFVIIa therapy on blood loss as well as on morbidity and mortality when it is used either before or very soon after onset of hemorrhage rather than as a therapy of last resort in patients who have already lost massive amounts of blood.

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