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Recombinant factor VIIa (NovoSeven RT) use in high risk cardiac surgery☆

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Abstract

Objective: The use of recombinant factor VIIa (rFVIIa) (NovoSeven RT®) to establish hemostasis during massive perioperative bleeding in cardiac surgery has been explored in several retrospective studies. While early results are promising, a paucity of data leaves many questions about its safety profile. We sought to further define its use and associated outcomes in a large cohort study at a single institution. **Methods:** A retrospective cohort study design was used, in which 236 patients received rFVIIa for bleeding after cardiac surgery. These patients were matched with a cohort of 213 subjects, who had similar operations during the same period of time. Primary end points included thrombo-embolic events, mortality, incidence of re-operation, use of blood products, and patient disposition at 30 days. Statistical significance was assessed at $p < 0.05$. **Results:** There was no statistically significant difference in the incidence of stroke (3.4%, 1.9%; $p = 0.32$), renal failure (8.5%, 7.0%; $p = 0.57$), or 30-day mortality (7.7%, 4.3%; $p = 0.14$) between the rFVIIa and the control groups, respectively. The rFVIIa group did experience a higher rate of re-operation for bleeding (11.0%, 1.9%; $p = 0.0001$) and had a two-fold increase in the use of each of the following: cryoprecipitate, fresh-frozen plasma, platelets, and packed red blood cells, relative to the control group ($p < 0.00001$). **Conclusions:** rFVIIa is an effective hemostatic agent for intractable bleeding in high-risk cardiac surgery with an acceptable safety profile. rFVIIa does not appear to be associated with increased postoperative complications, including thrombo-embolic events and death.

Keywords: rFVIIa; Factor VII; Thrombo-embolic; Hemorrhage; Re-exploration; Mortality

1. Introduction

Massive postoperative bleeding is one of the most common and the most feared complications of high-risk cardiac surgery. Mediastinal drainage in excess of 1000 ml has been reported to occur in nearly 30% of cases [1]. These high-volume blood losses frequently require the cardiac surgeon to consider re-exploration. This is a difficult decision, as a return to the operating room carries significant morbidity. In one series of coronary artery bypass graft (CABG) patients, length of stay nearly doubled and risk of mortality tripled with re-exploration [2]. Furthermore, re-exploration does not reveal a surgically repairable source of bleeding in up to 50% of cases [3].

At present, the initial treatment of postoperative bleeding is the administration of blood products. However, this is not inconsequential. One study on long-term survival after cardiac operation revealed that transfusion is associated with a 70% increase in mortality [4]. A recent study of blood conservation in the cardiac surgery population observed an increased incidence of stroke, myocardial infarction (MI), and prolonged ventilation among transfused patients [5]. These findings have prompted cardiac surgeons to explore the off-label use of recombinant factor VIIa (rFVIIa) as an alternative hemostatic agent for postoperative bleeding.

Introduced in 1983, rFVIIa was first described by Hedner and Kisiel for the treatment of bleeding in two hemophilia A patients [6]. It has since been approved by the Food and Drug Administration (FDA) for bleeding in hemophiliacs with antibodies to factors VIII and IX, and, additionally, in some European countries for those with factor VII deficiency and Glanzman thromboastheneia [7,8].

To date, there are two large retrospective reviews on the use of rFVIIa for perioperative bleeding in cardiac surgery. While early results appear promising, there are many concerns about its efficacy and safety profile [9,10]. This was highlighted in 2008 when a Canadian Consensus group reviewed the use of rFVIIa in cardiac surgery and concluded that 'rigorous studies are needed to clarify its (rFVIIa) risk—benefit profile in surgery patients' [11].

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The aim of the present study was to further define the safety profile and effectiveness of rFVIIa in the high-risk cardiac surgery patient.

2. Materials and methods

2.1. Patients

A retrospective review of 236 patients, who received rFVIIa for bleeding after cardiac surgery at Spectrum Health Hospital between January 2005 and February 2010, was conducted. These patients were matched with a cohort of 213 patients, who had similar operations during the same period of time. Data collected included patient demographics, adverse events, mortality, use of blood products, and dose of rFVIIa. Postoperative renal failure, cerebrovascular accident (CVA), and MI were defined according to the Society of Thoracic Surgeons' guidelines. European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores were assigned to patients in each group. This study was approved by the Spectrum Health Institutional Review Board.

2.2. Criteria for administration of rFVIIa

Our institutional policy dictates that rFVIIa can be used for persistent, massive, and life-threatening hemorrhage in non-hemophiliac patients in a non-futile setting, with an arterial pH >7.2. Our hospital advises that additional doses can be administered 15–20 min after the initial dose, if no response is observed.

2.3. Statistical analysis

The sample size for the study was determined by reviewing the records of all patients who received rFVIIa at our institution from January 2005 through February 2010, and matching them with control patients over the same time period. Summary statistics were calculated. Age and ejection fraction are presented as the mean ± standard deviation (SD), EuroSCORE, vent hours, and intensive care unit (ICU) hours are presented as the median and the range, and nominal data are presented as a percentage. Comparisons between groups for quantitative variables were performed using the *t*-test, and for ordinal variables using the Mann–Whitney test. Nominal variables were evaluated using the chi squared (χ^2) test. Significance was assessed at $p < 0.05$.

3. Results

3.1. Patient demographic and clinical information

Table 1 highlights the demographic and clinical characteristics of our patient population. Additive and logistic EuroSCOREs were statistically significantly higher for the control group compared with the rFVIIa cohort. However, both groups were considered high risk with an average additive score >6 [12]. The two groups were relatively similar for all of the other variables tested. Table 2 describes the type of operative cases. The majority of procedures involved CABG surgery: 51.7% in the rFVIIa group and 53.5% in the control group. Over half of the cases in both groups were elective (Table 3).

Table 1. Patient demographics.

Characteristic	rFVIIa group	Control group	*p*-value
Male (%)	173/236 (73.3%)	155/213 (72.8%)	0.90
Age (year)[a]	66.0 ± 13.3	65.6 ± 13.1	0.78
Smoker (%)	48/105 (45.7%)	65/133 (51.1%)	0.63
Diabetes (%)	49/236 (20.8%)	49/213 (23.0%)	0.57
NYHA (class III + class IV)[d]	101/136 (74.3%)	116/155 (74.8%)	0.91
Left main disease (>50%)	39/236 (16.6%)	35/212 (16.5%)	0.98
Ejection fraction (%)[a]	51.3 ± 11.3	53.4 ± 12.1	0.07
EURO score (additive)[b,c]	7.0 (0, 20)	8.0 (0, 19)	0.02
EURO score (logistic, %)[b,c]	8.4 (0.9, 88.7)	10.3 (0.9, 80.2)	0.01

[a] Mean ± SD.
[b] EURO, European System for Cardiac Operative Risk Evaluation.
[c] Median (range).
[d] NYHA, New York Heart Association.

Table 2. Type of surgery.[a]

Characteristic	rFVIIa group	Control group
CABG[b]	48/236 (20.3%)	45/213 (21.1%)
CABG + other	7/236 (3.0%)	6/213 (2.8%)
CABG + valve	31/236 (13.1%)	34/213 (16.0%)
CABG + valve + other	36/236 (15.3%)	29/213 (13.6%)
Other	17/236 (7.2%)	14/213 (6.6%)
Valve	42/236 (17.8%)	41/213 (19.2%)
Valve + other	55/236 (23.3%)	44/213 (20.7%)

[a] There was no statistically significant difference in the distribution of the type of surgery between the rVIIa group and the control group (χ^2 test, $p = 0.96$).
[b] CABG – coronary artery bypass graft.

Table 3. Surgery classification.[a]

Characteristic	rFVIIa group	Control group
Elective (%)	125/236 (53.0%)	122/213 (57.3%)
Urgent (%)	74/236 (31.4%)	72/213 (33.8%)
Emergent (%)	35/236 (14.8%)	18/213 (8.5%)
Emergent salvage (%)	2/236 (0.8%)	1/213 (0.5%)

[a] There was no statistically significant difference in the surgery classification between the rVIIa group and the Control group (χ^2 test, $p = 0.10$; data for emergent and emergent salvage were combined into one group).

3.2. Patient outcomes

Patient outcome data are described in Table 4. Eight (3.4%) of the rFVIIa patients had a CVA. Two of these were hemorrhagic strokes and one patient experienced stroke symptoms, but expired before a head computed tomography (CT) could be attained. We presumed that this patient had an ischemic stroke. There were no MIs, deep venous thromboses (DVTs), or pulmonary emboli (PEs). Importantly, there was no significant difference in the incidence of thrombo-embolic events or acute renal failure between the two groups. There was a higher incidence of pneumonia in the rFVIIa group and this approached significance with a *p*-value of 0.05. Hours in the ICU as well as hours on the ventilator were statistically significantly longer for the rFVIIa group compared with the control group.

Table 4. Clinical outcomes.

Outcome	rFVIIa group	Control group	*p*-value
Pneumonia (%)	16/236 (6.8%)	6/213 (2.8%)	0.05
30-day mortality (%)	18/235 (7.7%)	9/210 (4.3%)	0.14
Rebleed (%)	26/236 (11.0%)	4/213 (1.9%)	0.0001
Surgically repairable (%)[b]	9/24 (37.5%)	4/4 (100%)	0.03
Vent hours[a]	15.0 (2.2, 960)	6.9 (1.2, 947.3)	<0.00001
ICU hours[a]	68.6 (8.1, 2121.9)	22.7 (8, 1226.7)	<0.00001
Stroke (%)	8/236 (3.4%)	4/213 (1.9%)	0.32
Ischemic (%)	6/8 (75.0%)	4/4 (100%)	0.52
Hemorrhagic (%)	2/8 (25.0%)	0/4 (0%)	0.52
Renal failure (%)	20/236 (8.5%)	15/213 (7.0%)	0.57
Dialysis (%)	11/233 (4.7%)	8/212 (3.8%)	0.62

[a] Median (range).
[b] Two patients were taken back to the operating room for sternal replating and had no ongoing bleeding.

Mortality rates were not significantly different for the rFVIIa and control groups, as demonstrated in Table 4 (7.7%, 4.3%; $p = 0.14$). There were no differences between the two groups with regard to rates of disposition (transfer to an extended care facility vs discharge home) and re-admission at 30 days.

3.3. Blood product administration, re-operation, and rFVIIa dose

Patients received a total of 1.2–20.0 mg of rFVIIa (6.5 ± 3.8 mg, mean $\pm$ SD) after bleeding had not responded to traditional therapy [i.e., packed red blood cells (RBCs), cryoprecipitate (cryo), fresh-frozen plasma (FFP), and platelets]. The majority of patients received a single dose of rFVIIa, although some received one or two additional doses.

Of the patients who received rFVIIa, 26 (11.0%) required re-exploration for persistent postoperative bleeding. This was a statistically significant finding compared with the control group, which only had four (1.9%) re-operations for persistent bleeding. In addition, the percentage of surgically repairable re-bleeding events was statistically significantly higher in the control group. The use of each of the blood products was significantly higher in the rFVIIa group (Fig. 1).

Patients who received $\leq$5 mg rFVIIa vs patients who received >5 mg rFVIIa were compared. There were no significant differences found for incidence of pneumonia, renal failure, 30-day mortality, ICU hours, or ventilator hours. The higher dose group received significantly more platelets than the lower dose group (11.9 ± 10.7 mg vs 7.8 ± 7.8 mg); however, the use of FFP, cryo, and RBC was not higher in this cohort (data not shown).

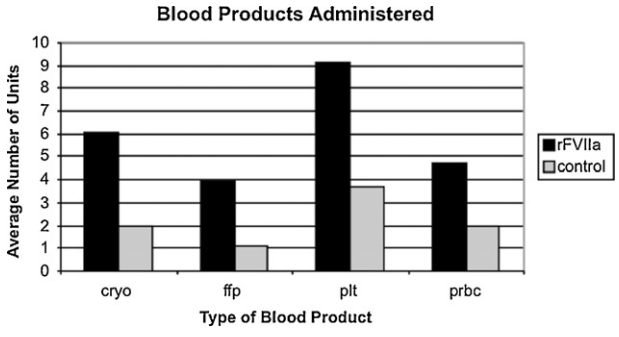

Fig. 1. Blood products administered. The rFVIIa cohort had a two-fold increase in the use of each of the following: cryoprecipitate (cryo), fresh frozen plasma (ffp), platelets (plt) and packed red blood cells (prbc), relative to the control group ($p < 0.00001$). This finding represents the addition of total blood products administered, both before and after administration of rFVIIa.

4. Discussion

The off-label use of rFVIIa has been of particular interest in the cardiac literature, where postoperative bleeding is a frequent source of increased morbidity and mortality. To date, there are two large multi-institutional retrospective reviews that address the safety and efficacy of this drug. While these studies are promising, their findings are limited, as they do not compare their results to a matched cohort [9,10]. Our research addresses this void. The aim of the present study is to further define the safety profile and efficacy of rFVIIa in the high-risk cardiac surgery patient by comparing outcomes to a control group at a single institution. We found that patients who received rFVIIa had no statistically significant increase in thrombo-embolic events, renal failure, or mortality. The rFVIIa cohort did have a significantly higher rate of re-operation for bleeding, a two-fold increase in the use of blood products, and, more frequently, had pulmonary complications.

In a retrospective review of 8586 CABG patients, re-exploration for postoperative hemorrhage was required in 3.6% of cases. Importantly, these patients had an in-hospital mortality of 9.5%, which was nearly triple the rate compared with those who did not require this intervention [2]. In our study, 26 patients (11%) who received rFVIIa required re-exploration for bleeding, which was significantly higher than the control group. Patients with massive bleeding received rFVIIa only if hemorrhage continued after aggressive administration of blood products (Fig. 1). Given this protocol, we believe the rFVIIa cohort had a more severe bleeding diathesis, and, therefore, the higher re-exploration rate was not an unexpected outcome.

Among our patients who returned to the operating room, a surgically repairable source of bleeding was not identified in 58% (17) of cases. This is consistent with the literature [3], and should be expected, as the etiology of bleeding in the post-bypass patient is often due to an inherent coagulopathy [8,13]. Administration of blood products remains the primary treatment modality for postoperative hemorrhage; however, recent studies question their safety. One study of 2000 patients revealed that the transfused cardiac surgery patient had a 15% 5-year mortality vs 7% for the non-transfused patient. When corrected for co-morbidities, this same group of patients had a 70% increased long-term mortality [4]. Another study of 5123 cardiac surgery patients associated the administration of four or more units of fresh-frozen plasma or the transfusion of RBCs with prolonged mechanical ventilation [14]. We observed increased pulmonary complications in our rFVIIa cohort, who received twice the amount of blood products (Fig. 1). The association between time on the ventilator and ventilator-associated pneumonia (VAP) has been well established, and, therefore, the increased incidence of pneumonia in the rFVIIa group comes as no surprise. We think it is reasonable to attribute our pulmonary morbidities at least partly to the administration of blood

products and not as a result of rFVIIa administration. These findings emphasize the fact that we should be using traditional blood products sparingly, and that their use does not come without complications.

89 percent of our patients, who received rFVIIa for refractory postoperative hemorrhage, did not require re-exploration. We surmise that these patients achieved hemostasis secondary to rFVIIa administration. Furthermore, we believe transfusion of blood products is reduced after administration of rFVIIa. Unfortunately, due to a lack of chronologic data in our hospital records, we are unable to prove this. However, other studies have demonstrated this outcome [9,10,15]. Given this information, our practice has changed. We tend to administer rFVIIa earlier, especially where risk of blood product use is high. This specifically includes patients with right-ventricular failure, pulmonary hypertension, or severe lung disease.

There is still concern that rFVIIa may lead to thrombo-embolic events; however, this has probably been over-stated. The largest safety review of the drug suggests that thrombo-embolic events occur in less than 1% of rFVIIa administrations [15]. In the cardiac literature, the rate of thrombo-embolic events is reported as higher. The Australian and New Zealand Haemostasis Registry reported a 4% thrombo-embolic event rate [9]. Others have reported a stroke rate as high as 12% [10]. A systematic review on rFVIIa in the cardiac literature reports an average thrombosis rate of 5.3%; half of these events presented as stroke [16]. These findings are unfortunately limited, as they are not compared with matched cohorts. We found no significant difference in the rate of thrombo-embolic events between the variable and control groups. There were eight strokes in the rFVIIa cohort, and there was no MI, DVT, or PE. Two of the strokes in the rFVIIa cohort were hemorrhagic and would, therefore, be difficult to attribute to the drug. The Canadian Consensus on the use of rFVIIa in cardiac surgery suggests that rFVIIa as a rescue drug for hemorrhage refractory to traditional blood products is appropriate. They suggest cautioned use in patients with predisposition to CVA [11]. We would agree that any prothrombotic agent should be used carefully in patients with risk factors for CVA, but we are not convinced that rFVIIa can definitively be linked to thrombo-embolic events.

To our knowledge, there are no data analyzing a link between rFVIIa and renal complications. In our study, patients who had a two-fold increase in creatinine over their hospital stay or had the new requirement of dialysis were classified as having acute renal failure (ARF). Our two patient cohorts did not vary significantly in the development of ARF. Furthermore, the number of patients necessitating dialysis did not vary significantly. We do not believe that the administration of rFVIIa has a harmful impact on kidney function. While our rate of renal failure in both groups was higher than the typical incidence of ARF in cardiac surgery patients, we believe it is fair to attribute this to the high-risk nature of our patients [17].

We found no clear relationship between adverse outcomes and dose. Interestingly, the patients who received a higher dose of rFVIIa dose received more platelets. This reflects the fact that rFVIIa has typically been used as a rescue drug at our institution. It is difficult to make any conclusions about rFVIIa dose in our study, but it does seem to reflect the thought that higher doses are not related to adverse outcomes.

Mortality rates at 30 days were not significantly different in the two patient cohorts. In both groups, the majority of patients died of cardiac complications, with neurologic and pulmonary complications accounting for most of the remainder. There is conflicting evidence on rFVIIa and mortality in the literature. In the absence of randomized control trials, this will be difficult to determine.

While this study was not designed to be a commentary on the economics of this drug, in the age of cost containment, it must be discussed briefly. In 2007, a 90 $\mu g\,kg^{-1}$ dose of NovoSeven RT® for an 80-kg male was $4500. A recent study by Toole et al. analyzing the economics of rFVIIa concluded that in the face of avoiding a re-operation, the drug can be administered without any 'appreciable increase in cost' [18]. A study completed in 1998 found that postoperative hemorrhage in the cardiac patients increased hospital costs by $11 266. These costs were largely attributed to blood transfusion and longer ICU and hospital stay [19]. This was duplicated in a recent German study where postoperative bleeding was not only associated with increased mortality (22.4%) but also substantially increased costs. Those authors recommended that mechanisms to effectively 'reduce postoperative hemorrhage in cardiac surgery are likely to have substantial cost-effectiveness potential' [20]. Early evidence appears to suggest that the use of rFVIIa does not place an increased burden on health-care systems and may actually have a favorable cost–benefit outcome. This relationship needs to be studied further, but we do not believe that rFVIIa costs should serve as a limitation to the use of this drug.

We believe that rFVIIa is an effective hemostatic agent with an acceptable safety profile. It does not appear to be associated with increased thrombo-embolic events, renal failure, or mortality. In our institution, rFVIIa has traditionally been used as a rescue drug. We believe that the earlier use of rFVIIa may be associated with decreased blood product administration and need for re-operation. At this point, prospective randomized control trials are needed to further define the safety profile of this drug.

5. Limitations

This study has several limitations, including its retrospective design. While this is one of the largest single-institution studies of rFVIIa in the cardiac literature, we did have nine cardiac surgeons involved in its 5-year production. This undoubtedly leads to variations in operative technique, triggers for administration of rFVIIa, and protocols for re-exploration. We must additionally question whether or not our study is underpowered. While there was a trend for higher mortality and stroke rates in the rFVIIa group, this finding was not significant. It is possible that a larger rFVIIa cohort would have changed this result. Furthermore, the rFVIIa cohort received twice the number of blood products. This makes it difficult to establish if the 89% rate of hemostasis after rFVIIa administration was exclusively secondary to the drug. It is clear that

randomized prospective trials are needed to further elucidate the use of the rFVIIa for postoperative hemorrhage in the cardiac surgery patient and to fully define the safety profile in this population.

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Appendix A. Conference discussion

Dr W. Gomes (*Sao Paulo, Brazil*): As you know, we are operating on sicker patients more frequently, with the associated bleeding risk. Transfusion can be as bad as the bleeding itself because of its associated early and late complications. And factor VII is a promising tool for trying to minimize the risk of these events.

So I have a straightforward question trying to summarize your presentation in fact. In my view, it might be helpful if you could give this drug earlier in these types of patients, so that it can have an impact on our clinical every-day practice. From your data can you predict or define a profile of patient that could benefit most from early administration of factor VII, therefore minimizing the risk of bleeding?

Dr Chapman: I think there is a group that benefits from early administration of factor VIIa. In fact, at our hospital our practice has changed. Knowing that there is a certain group of patients that is at particular risk of transfusion, those with significant lung disease or right ventricular failure, we tend to administer factor VII now much earlier if there is any evidence of bleeding, and in fact sometimes administer factor VIIa in the operating room at the end of the case.

Dr Gomes: So therapy postoperatively?

Dr Chapman: Right. So, yes, I think there is a group that would benefit from earlier administration.

Secondly I will address your (Dr Klein's) comment on cost. This drug is very expensive. At our hospital it costs about a dollar per microgram. In a typical 80 kg patient, that would be almost 5000 U.S. dollars. There have been several studies, however, that demonstrate that there is significant cost associated with postoperative hemorrhage, transfusion, and with going back to the operating room for re-exploration. Studies that have looked at the cost–benefit of administering factor VII and avoiding a trip back to the operating room demonstrate a possible cost–benefit of giving factor VII, and so I think this (factor VIIa cost) probably should not serve as a barrier.

Dr M. Klein (*Dusseldorf, Germany*): I'd like to give a comment. Everybody knows that the highest risk for bleeding is the cardiac surgeon himself. All the techniques we have in our hands to reduce postoperative bleeding should be in the management protocol. We should utilize the normal technologies to stop bleeding intraoperatively before we close the chest. It is very difficult I guess to have some guidelines as to what special therapy to use in what kind of patients, especially factor VII, because it's very, very expensive.

The comment I can give from my own experience is that we have to train our younger surgeons to operate more atraumatically and to be faster. We all know that on-pump time will influence bleeding tendencies in some patients and we need excellent management involving the anesthesiologists and perfusionists, if we are on ECC, to control bleeding tendencies in our patients.

Dr A. Wahba (*Trondheim, Norway*): I fully agree that factor VIIa is a very important tool for the cardiac surgeon in many situations. I just don't fully subscribe to your conclusion that there are no thromboembolic complications. You know that there are other trials that state that there may be embolic problems and it would seem obvious from the mechanism of action of the drug. So how did you look for thromboembolic complications in your trial?

Dr Chapman: We classified our thromboembolic events as either stroke, MI, PE or DVT. We did not have any of the latter three. We used the Society of Thoracic Surgeons' definitions to classify whether or not we had those events. Our strokes were all confirmed by CT scan and so that's how we classified the thromboembolic events.

One limit of this study may be that it is underpowered. I agree that we did have some thromboembolic events. And in our factor VII group, we had twice as

many strokes as we did in the control group. However, the *p* value did not approach conventional statistical significance. So it's possible if we had more patients that there would be a significant difference compared to our control cohort.

Dr K. Hampton (*Sheffield, United Kingdom*): Two very brief questions. In your 5-year cohort, how many surgical procedures were performed? What was the denominator?

Dr Chapman: We are a high-volume center. I don't know exactly what the total number of operations was, but I can tell you that the 236 patients that were included in the study comprised every single patient that received factor VII for intractable bleeding.

Dr Hampton: That's roughly one a week. So how many operations do you do a week?

Dr Chapman: I'm not sure.