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Low-dose recombinant factor VIIa for trauma patients with coagulopathy[☆]

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Accepted 26 March 2008

KEYWORDS

Trauma;
Coagulopathy;
Traumatic brain injury;
Thromboembolic complications

Summary

Introduction: Coagulopathy in injured patients is common and is generally treated with fresh frozen plasma (FFP). Response can be variable, thus complete correction may take hours and require large volumes of fluids. High-dose recombinant factor VIIa (FVIIa, Novoseven, Novo Nordisk, Bagsvaerd, Denmark) has been used off-label to treat severe coagulopathy following trauma. Expense has limited use. Recently, we began administering low dose FVIIa (1.2 mg) to patients with mild to moderate coagulopathy after trauma, hypothesising that it would be effective and safe.

Patients and methods: We retrospectively reviewed consecutive patients who received a low dose of 1.2 mg of FVIIa over a 2-year period. Factor VIIa is administered after approval by a gatekeeper at the discretion of the treating physician. Demographics, injury and laboratory data were abstracted as were indications for use, source of coagulopathy, effectiveness, and complications. A two-tailed paired *t*-test was used to determine significant changes in coagulation parameters and blood product utilisation.

Results: Eighty-one patients received 84 low doses of FVIIa. The mean age of the patients was 51 (± 22) with a mean ISS of 29 (± 11). Seventy-three per cent were male and 67% had a traumatic brain injury (TBI) as their primary injury. The aetiology of the coagulopathy in the study population included; TBI (40%), warfarin use (22%), and cirrhosis (13%). Mean prothrombin time (PT) fell from 17.0 s (± 3.2) to 10.6 s (± 1.4) ($p < 0.0001$). All patients had a good clinical response with no bleeding complications. Utilisation of packed red blood cells and fresh frozen plasma were significantly less in the 24 h after FVIIa administration as compared to the 24 h prior. Subsequent

[☆] Presented at the 65th Annual Scientific Assembly of the Eastern Association for the Surgery of Trauma, New Orleans, Louisiana, September 28, 2006.

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thromboembolic events were observed in 12 of the 81 patients (15%) and included; cerebrovascular accident (CVA) (6), mesenteric thrombosis (2), myocardial infarction (MI) (1), pulmonary embolism/deep venous thrombosis (PE/DVT) (2), and atrial thrombus (1). Only four of these events were thought to be related to the FVIIa administration, with two of the four contributing to a lethal outcome.

Conclusions: Low dose FVIIa rapidly and effectively treats mild to moderate coagulopathy following injury. This low dose (1.2 mg) FVIIa is the smallest available unit dose. It costs approximately the same as 8 units of plasma and may be cost-effective in patients who require high volume factor administration. Low dose FVIIa may be effective in coagulopathic trauma patients who are not in shock but require rapid normalisation of clotting function.

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Introduction

Coagulopathy is common in injured patients. Most typically, it is associated with severe haemorrhage and the dilutional coagulopathy that occurs as a result of massive transfusions and ongoing haemorrhage. Recombinant factor VIIa (FVIIa; Novoseven, Novo Nordisk, Bagsvaerd, Denmark) has been used as an adjunctive therapy for this form of coagulopathy in trauma patients on an off-label basis for several years.^{12,13} Numerous case reports and case series have been published describing the use of rFVIIa for this indication.^{7,12,13,17,20,25,26,33,34} Recently, a randomised prospective trial was published that demonstrated efficacy in blunt trauma patients in terms of blood product utilisation.⁵ Additional trials are currently underway in an effort to demonstrate that FVIIa is a safe and effective adjunctive treatment for patients with traumatic coagulopathy.

There are, however, a number of other aetiologies of more mild to moderate forms of abnormal coagulation in injured patients. Commonly, trauma patients have pre-morbid conditions, such as cirrhosis, or take medication, such as warfarin, that cause abnormalities of clotting. Patients with traumatic brain injury (TBI) may have abnormal coagulation simply as a result of the brain injury itself and the resulting release of tissue thromboplastin and abnormalities of fibrinolysis.^{7,8,12,22,43} Additionally, multiple organ dysfunction syndrome and sepsis, which are not uncommon sequelae of severe injury, may cause coagulopathies secondary to liver and bone marrow dysfunction.

In the injured patient, these more mild forms of coagulation dysfunction often require rapid reversal in order to prevent or attenuate bleeding or to allow for bedside or operative procedures to be performed safely. Typically fresh frozen plasma has been used to normalise coagulation in these patients, but may require large volumes and often take several hours to administer and may not fully correct the coagulopathy. Additionally, there are infectious risks asso-

ciated with blood product administration as well as the risk of fluid overload secondary to large volume administration. Some patients, most typically Jehovah's Witness patients, will not accept any blood products, which leaves clinicians with little in their armamentarium to normalise coagulation.

The typical doses of FVIIa for use in trauma patients with severe coagulopathy and haemorrhagic shock range from 50 to 200 mcg/kg.^{5,14,17,25,26,40} The lowest unit dose of FVIIa available is a 1.2 mg vial. We began administering FVIIa in this lower dose to injured patients who required rapid reversal of mild to moderate coagulopathy at our institution in 2004. We hypothesised that low dose FVIIa is a safe, rapid, and effective therapy to reverse mild to moderate coagulopathy in injured patients.

Patients and methods

At the R Adams Cowley Shock Trauma centress (STC), FVIIa is requested by the treating attending surgeon, intensivist, or anaesthetist. Release by the pharmacy requires approval of an institutional gatekeeper (TMS, RPD, JRH). The gatekeepers monitor usage and determine dose to be given based on provided clinical information. The low dose (1.2 mg) FVIIa is approved for patients who require rapid reversal of mild to moderate coagulopathy, but are not in shock. The drug is then reconstituted and administered according to the manufacturer's instructions. A database is maintained by the gatekeepers of all patients in our institution to whom FVIIa is administered. Thromboembolic prophylaxis is provided for all patients in accordance with an institutional protocol that uses immediate mechanical prophylaxis in all patients on admission to the in-patient unit and low molecular weight heparin as soon as a stable haematocrit is achieved or 72 h from admission in patients with TBI or spinal cord contusion.

Following approval by the University of Maryland Institutional Review Board, patients who received

1.2 mg as a single dose at STC were identified from the database. The medical records of these patients were then reviewed and demographics, injury-specific data, laboratory values, blood product utilisation, and timing of FVIIa administration were abstracted. A two-tailed paired *t*-test was used to determine significant changes in coagulation profiles before and after administration, as well as differences in blood product utilisation. A *p* value of <0.05 was considered significant for all statistical tests.

Results

From June 2004 to 2006, 81 patients were identified who received 84 low doses (1.2 mg) of FVIIa at our institution. The three patients who received more than one dose of FVIIa were administered the second dose several days (>72 h) after the first for correction of a new or recurrent coagulopathy. Table 1 presents the demographics of the patients in this study group. The majority of patients were male and mean injury severity score (ISS) was 29 (± 11). Mortality was 31% in this study population. Mechanism of injury was blunt in 69 patients (85%) (35 from falls, 20 from motor vehicle collisions, 6 pedestrians stuck, 6 assaults, and 2 motorcycle crashes). Four patients (5%) sustained penetrating injuries and 8 patients (10%) were given FVIIa during readmissions to the trauma centre. The mean weight of the patients was 81.0 kg (± 23.2 , range 48–191) and the mean dose administered was 15.6 mcg/kg (± 4.2). Sixty-seven per cent of patients had a traumatic brain injury (TBI) as their most severe primary injury.

The aetiology of the coagulopathy in this patient population included TBI (40%), pre-injury warfarin use (22%), cirrhosis (13%), multiple organ dysfunction syndrome (5%), ongoing haemorrhage (5%), pre-injury antiplatelet medication (4%), and uraemia (1%). Five per cent had multiple causes of their coagulopathy and 4 patients (5%) were administered low dose FVIIa secondary to refusal to accept blood products due to religious beliefs (Jehovah's Witnesses). Fig. 1 depicts the timing of administration of FVIIa in this patient population.

In this cohort, the most frequent primary indication for low dose FVIIa administration was rapid reversal of coagulopathy in 54 patients with TBI. Sixty-one per cent of these had mild coagulopathy from the TBI itself and 30% were intentionally anticoagulated with warfarin prior to their injury. Seven per cent of these patients with TBI had coagulation abnormalities secondary to cirrhosis. Low dose FVIIa was administered to 11 mild to moderately coagulopathic patients who required urgent operative inter-

Table 1 Demographics of study population

	Mean	S.D.
Age (years)	51	22
ISS	29	11
TRISS	0.728	0.299
LOS (days)	17.1	18.2
ICU LOS (days)	9.9	9.9
Dose (mcg/kg)	15.8	4.2
	<i>n</i>	%
Gender		
Male	59	73
Female	22	27
Primary anatomic injury		
TBI	54	67
LE Fx	7	9
Spine	4	5
Multiple	4	5
Other	12	15
Discharge disposition		
Died	25	31
Rehabilitation facility	52	64
Home	4	5

ISS: injury severity score; LOS: length of stay; ICU: intensive care unit; TBI: traumatic brain injury; LE Fx: lower extremity fracture.

vention for fracture stabilisation. Four patients with coagulopathy from multiple organ dysfunction syndrome (MODS) and ongoing haemorrhage also received low dose FVIIa. These patients were critically ill patients in the intensive care unit who failed to respond to conventional therapy and large volume plasma administration. These patients required invasive procedures, such as tube thoracostomy or oesophagogastrosopy for upper gastrointestinal bleeding. Four additional patients with platelet dysfunction from either anti-platelet medication or uraemia were given 1.2 mg of FVIIa. Despite the obvious abnormalities of clotting seen in these patients, the coagulation profiles (PT and INR) of these patients on antiplatelet medication (aspirin and clopidogrel) and with uraemia were

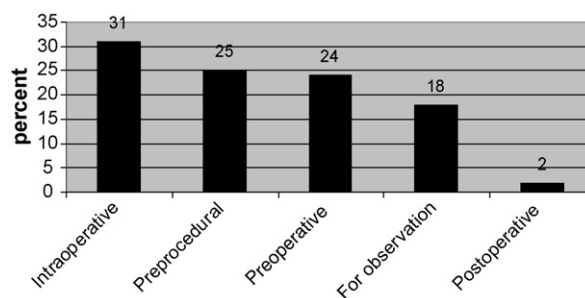


Figure 1 Timing of administration of FVIIa.

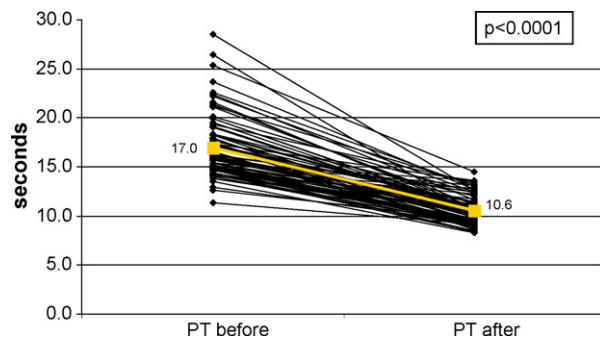


Figure 2 Prothrombin time before and after FVIIa administration.

relatively normal, as would be expected. Despite the normal PT and INR, these patients, had a favourable clinical response to FVIIa administration. An additional 4 of the 81 patients in this study had normal coagulation profiles and were not thought to be coagulopathic, but required surgical intervention that would potentially subject them to significant bleeding and will not take blood products secondary to religious beliefs.

All patients had a good clinical response to FVIIa administration with no procedural or operative bleeding complications reported after low dose FVIIa administration. Coagulation profiles were available for all except for one patient before and after FVIIa administration. Mean prothrombin time (PT) was 17.0 s (± 3.2 , range 12.6–28.5) prior to FVIIa administration and was 10.6 s (± 1.4 , range 8.3–14.5) after administration. Two-tailed paired *t*-test demonstrated a *p* value of < 0.00001 for change in PT. Fig. 2 graphically depicts this change. Mean international normalised ratio (INR) was 1.9 (± 0.67 , range 0.9–4.7) prior to administration and was 0.8 (± 0.21 , range 0.4–1.4) after ($p < 0.0001$).

Packed red blood cell (PRBC) and FFP administration was statistically less in the 24 h following 1.2 mg FVIIa than in the 24 h preceding ($p = 0.0019$ and $p < 0.0001$, respectively). There was no statistically significant difference in number of units of

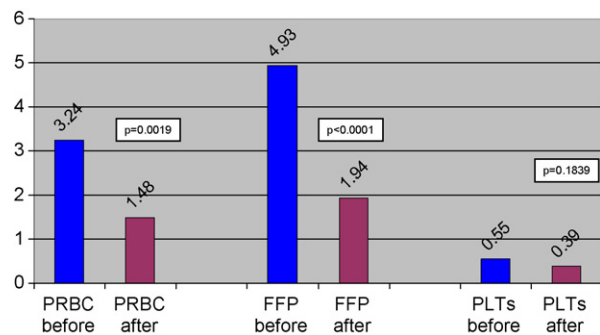


Figure 3 Mean units of blood products transfused 24 h before and after FVIIa administration.

platelets (PLT) transfused before and after FVIIa administration. Fig. 3 demonstrates the blood product utilisation in this study population.

The incidence of thromboembolic complications in this study population was 14.8%. There were 12 thrombotic complications observed. These included 6 cerebrovascular accidents (CVA), 2 mesenteric thromboses with infarction, 1 pulmonary embolism (PE), 1 deep venous thrombosis (DVT), 1 myocardial infarction (MI), and 1 atrial thrombus. Four of these events were judged to have a medium or high association with the FVIIa dose because the timing of administration closely preceded the event, and because of a lack of other potential causes. Two of the six patients who had CVAs had blunt cerebrovascular injuries, one had severe atherosclerotic disease of the carotid arteries, and three had infarctions in the area of herniated brain secondary to decompressive craniectomies. Both patients with mesenteric thrombosis had major mesenteric vascular injuries and the patient with a pulmonary embolism had a pre-morbid history of PE and DVT and was readmitted with a new PE 20 days after discharge following nonoperative treatment of TBI. Seven of the patients with thromboembolic complications died, but in only two of the patients was the thromboembolic event thought to be related to mortality.

Discussion

Recombinant factor VIIa was originally described for the treatment of bleeding in haemophiliacs with inhibitors.²¹ Since that time, its use has extended to a wide variety of patient populations with active bleeding, bleeding diathesis, and risk of recurrent or refractory bleeding in both elective and emergent circumstances. FVIIa has been widely used on an off-label basis for the treatment of coagulopathy in trauma patients since the first report of its use in 1999.²⁵ Since that time the literature has been replete with case reports and case series describing its use in coagulopathy associated with haemorrhagic shock following injury.^{7,12,13,17,20,25,26,33,34} Additionally, case reports and series have been published of FVIIa use in coagulopathic patients at risk of bleeding as well.^{3,16,32,37,41,42,49,47} FVIIa use has been described in patients taking antiplatelet medications, with cirrhosis, on warfarin, and with thrombocytopenia.^{1,3,4,9,11,14,15,18,27,30,36–38,41,42,47,50,51}

In the trauma population, often these pre-morbid or mediation-related bleeding diatheses and coagulopathies are present. Additionally, injuries such as TBI can directly cause mild to moderate coagulopathies.^{7,8,12,43} In these patients, rapid reversal and normalisation of the coagulation cascade is essential

in order to allow for intrinsic clotting and bleeding cessation and to prevent procedural and operative bleeding complications. We have found that this low dose rapidly and effectively reverses mild to moderate coagulopathy in these patients. Uniformly, the PT and INR normalise, but more clinically relevant is the lack of bleeding associated with the invasive procedures performed in these patients. PRBC and plasma utilisation is significantly decreased following FVIIa administration, as well.

FVIIa is expensive and this high cost has, to some degree, limited widespread use. In the doses described for haemorrhagic shock, the acquisition cost in our institution ranges from \$3240 USD for a single 50 mcg/kg dose to \$12,960 USD for a 200 mcg/kg dose. In coagulopathic patients without active haemorrhage, the literature describes a wide range of doses utilised; from 5 to 120 mcg/kg for cirrhotics undergoing "minor procedures" to doses of 40–120 mcg/kg in patients requiring neurosurgical intervention.^{2,10,24,30,42,44} The patients described in this study with mild to moderate coagulopathy were treated with a single, non-weight based dose of 1.2 mg of FVIIa. This is the smallest unit dose available and costs approximately \$1000 USD. At our institution, this is equivalent to approximately 8 units of plasma at \$120 USD per unit for acquisition and administration cost. As part of an ongoing project, we have determined that this dose of FVIIa will normalise the INR in a patient receiving warfarin for approximately 6 h, or 3 half-lives of the drug (J. Hess, personal communication, 2006). One small prospective study from Italy used the 1.2 mg dose in cardiac surgery patients and demonstrated a reduction in postoperative bleeding.⁴⁵ The correction of coagulation that occurs following low dose FVIIa administration is extremely rapid and does not subject the patient to the risks associated with high volume administration of plasma, such as fluid overload and congestive heart failure, particularly in older patient populations and those with preexisting cardiac disease.

In this cohort the most frequent indication for low dose FVIIa administration was rapid reversal of coagulopathic patients with TBI. At our institution, neurosurgeons are reluctant to place any monitoring device or to perform emergency craniotomy for evacuation of mass lesions without complete normalisation of the coagulation profile. Many of these patients fail to normalise their coagulation profiles despite aggressive plasma administration. The 1.2 mg dose of FVIIa rapidly and effectively accomplishes this and allow for prompt intervention. Plasma is then administered concomitantly, but slowly, to allow for ongoing normalisation of coagulation after the termination of the FVIIa effect.

Successful reversal of TBI-related coagulopathy with FVIIa administration has been reported, but generally at doses that are much higher than used in our patient population.^{39,42} Additionally, a number of patients in our study population with elevated PT secondary to warfarin use were administered low dose FVIIa who did not require intervention. In these cases, the FVIIa was used to rapidly correct the coagulation abnormality to prevent worsening of the patient's primary injury secondary to lack of intrinsic clotting. A number of case reports have similarly documented successful use of FVIIa for rapid reversal of warfarin therapy in the setting of both traumatic and nontraumatic intracranial haemorrhage.^{6,15,30,46}

Another frequent use of low dose FVIIa in our cohort was in mild to moderately coagulopathic patients who required urgent operative intervention for fracture stabilisation. Several of these patients were older and at risk for congestive heart failure. In these patients, 1.2 mg of FVIIa rapidly corrected their coagulation abnormalities without rapid large volume administration of plasma that might subject them to fluid overload and subsequent respiratory compromise.

The subset of patients in whom we have used low dose FVIIa is in patients without will not take blood products secondary to religious beliefs but require operative intervention that would subject them to risk of significant haemorrhage. The use of FVIIa in injured Jehovah's Witness patients has previously been described at our institution, as well as in others.^{19,23,48} Other studies have looked at prophylactic FVIIa use in noncoagulopathic patients and demonstrated reductions in operative blood loss and transfusion requirements.^{16,31} All of the Jehovah's Witnesses in this study who received FVIIa for prevention of excessive surgical bleeding had a good clinical response and all but one, who was severely injured, were discharged to home without complications.

Despite the effectiveness of this approach in correcting mild to moderate coagulopathy in injured patients, there was a real risk of thromboembolic events. The thromboembolic complication rate was nearly 15% in this study population. Although most of these complications were not thought to be directly related to the FVIIa administration, some likely were. FVIIa is a powerful procoagulant and one randomised study of patients receiving FVIIa for intracerebral haemorrhage demonstrated an increased incidence of thromboembolic events.³⁵ The prospective randomised trial in trauma patients failed to demonstrate a difference in thromboembolic events in patients who received the study drug versus placebo.⁵ The patients in the trauma trial

were younger than those in the trial of intracerebral haemorrhage however, which may have accounted for some of the differences. The patients in this current study were older than those in the study by Boffard et al. (51 vs. 38 years) largely due to the large percentage of older patients on warfarin. A recent systematic review that looked at clinical studies in which FVIIa was used reported a 1–2% incidence of thrombotic complications.²⁸ Another study which reviewed safety data from company sponsored clinical trials revealed a thrombotic adverse event rate of 5.3% which was not different from placebo-treated patients.²⁹ A study that has recently been published from our institution has examined this association of thromboembolic events and FVIIa administration at all doses. Overall, there was a 9% incidence of these events, with a 3% incidence of complications thought to be directly associated with FVIIa administration.⁴⁹

There are certainly significant limitations to this study. First and foremost, we were unable to identify a control group to match this diverse patient population. This lack of a control group makes determination of efficacy impossible. We have been able to demonstrate a decrease in blood product utilisation following administration, but cannot determine what the outcome may have been in these patients had conventional therapy alone been used. Clearly blood product utilisation would be expected to be highest in the 24 h immediately following admission in all injured patients and therefore this effect cannot be attributed solely to the FVIIa administration in those patients who received the drug soon after admission. In those patients who received FVIIa later in their hospital course, the decreases in blood product utilisation should be a valid measure of efficacy. Additionally, we were able to demonstrate laboratory normalisation following administration of low dose FVIIa, but are well aware that a statistically significant decrease in coagulation profile does not necessarily correlate with correction of in vivo coagulopathy. Second, we were unable to obtain data concerning the rapidity of intervention following FVIIa administration that we feel is one of the great advantages of this approach to the mild to moderately coagulopathic patient. Third, the lack of an appropriate control group in this current study makes it impossible to determine what the risk of thromboembolic events would be without FVIIa administration.

Conclusions

This case series is simply designed to detail our successful experience with a novel therapeutic

approach to a difficult and frequent clinical dilemma. Low dose FVIIa administration may be beneficial in patients with these mild to moderate coagulopathies who require rapid and effective correction of their coagulation profile. The cost of this intervention is equivalent to approximately 8 units of plasma. Low dose FVIIa administration does not subject the patient to high volumes of fluid or the risks of blood product administration and allows for almost instantaneous reversal of the coagulopathy. Additionally, there is a certain percentage of patients that despite high volume factor administration fail to completely correct their coagulopathy. Low dose FVIIa uniformly normalises the prothrombin time in these patients. The high number of thromboembolic complications, however, are concerning. Clearly, FVIIa, even at these low doses, should be administered with extreme caution in patients at risk of thromboembolic events.

Conflict of interest statement

Drs. Stein, Dutton, and Scalea have received research funding from Novo Nordisk, Inc., the manufacturers of NovoSeven. Dr. Dutton has served as a consultant to Novo Nordisk for research study design, and has been a member of their speaker's bureau. None of the authors holds any financial interest in Novo Nordisk.

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