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The use of factor VIIa in haemorrhagic shock and intracerebral bleeding

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KEYWORDS

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Summary Factor VIIa is a revolutionary new pharmaceutical that promises to change the anaesthesia and critical care approach to major trauma. It is an extremely potent pro-coagulant agent, and while it enables haemostasis at the site of tissue injury, it also has the possibility of producing life-threatening thromboembolic complications. New data regarding FVIIa use is published almost every month, leading to a rapidly evolving clinical understanding of the potential indications, and potential pitfalls, of off-label use. Determination of appropriate practice, including the ability to judge the risks and benefits of FVIIa therapy for individual cases, is still some years in the future, and will depend in large part on clinical trials which are just getting underway.

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Introduction

Recombinant human coagulation factor VIIa (FVIIa) may represent an exciting new development in trauma care. An intravenous agent that rapidly – but safely – reverses coagulopathy and promotes haemostasis would be enormously useful to clinicians. FVIIa, developed initially for use in haemophiliacs, may be just that agent. In this manuscript, we will provide a brief description of the pharmacology and historical development

of FVIIa, review the side effects and contra-indications to its use, and discuss current and future applications to the trauma population.

Background and historical development

Factor VIIa (NovoSevenTM) was developed by Novo Nordisk specifically for the treatment of haemophiliacs who had developed antibodies to Factor VIII.⁹ It was licensed for this purpose in Europe in the 1990s, and in the US in 1999. Since introduction, approximately 1 million doses have been prescribed to patients with haemophilia, with reported side effects and complications no different from the

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untreated baseline. The drug is considered to be safe and effective enough in this patient population that auto-injectors are now approved in Europe for home administration of FVIIa.

Observation of the clinical effects of FVIIa has led to a new understanding of *in vivo* coagulation, and the development of new theories of how the haemostatic balance is maintained.¹⁷ Factor VII is the only human clotting factor that circulates normally in the activated form. Its presumed role in the clotting cascade is to serve as the 'trip wire' for clot formation. FVIIa reacts with tissue factor exposed in injured blood vessels to initiate platelet activation and form small amounts of thrombin at the point of intimal injury. The rest of the clotting cascade then occurs on the surface of the platelet, adherent to the injured area, resulting in a burst of thrombin production and the conversion of fibrinogen to fibrin. FVIIa in pharmacologic doses is also thought to be capable of reacting with the activated platelet itself, to produce a thrombin burst even in the absence of other clotting factors, and to inhibit fibrinolysis in the vicinity of newly formed clots.

Factor VIIa has been used off-label almost since its release, for a wide variety of congenital and acquired coagulopathies. The first published off-label use of FVIIa in trauma occurred in 1999, in Israel, in a soldier bleeding to death from multiple injuries sustained in a terrorist attack.¹⁰ He was *in extremis* in the operating room with ongoing coagulopathic bleeding secondary to shock, despite massive transfusion. A single large dose of FVIIa restored clinically normal coagulation, allowed the completion of emergency surgery and resuscitation, and contributed to his survival. Since that time, there have been numerous case reports describing the use of FVIIa to control bleeding in injured patients.^{14,19,8} The largest published case series to date is from our own institution, describing 81 patients treated with FVIIa for acute haemorrhagic shock, coagulopathy related to traumatic brain injury, and treatment-resistant coagulopathies developing in the intensive care unit.⁴ The only prospective trauma trial concluded to date was completed in 2004 and published in 2005, and is reviewed in detail below.¹

Since the publication of these reports, interest in FVIIa for trauma patients has increased steadily, as has the number of patients treated off-label. Multi-center prospective research trials are underway to study the efficacy of FVIIa in a variety of trauma-related populations, including patients with acute haemorrhagic shock, patients with bleeding related to traumatic brain injury (TBI), and patients taking anticoagulant drugs prior to injury. At the same time, more safety data is accumulating from

anecdotal case series and prospective trials in other disciplines.

Factor VIIa for haemorrhagic shock

The most obvious use for a potent pro-coagulant, such as FVIIa, is in patients who are in immediate danger of exsanguination. Severe haemorrhagic shock is characterized by progressive end-organ ischemia and the "lethal triad" of coagulopathy, hypothermia and acidosis.⁶ Death can occur even in the presence of massive resuscitation with red blood cells (RBCs), plasma, and platelets. Because the normal composition of whole blood cannot be adequately made up with transfused products, the patient with ongoing haemorrhage will eventually reach a point of circulatory system failure that becomes irreversible, even with adequate intravenous access and aggressive transfusion.⁵ This pathophysiology requires that successful resuscitation from haemorrhagic shock be focused specifically on the rapid diagnosis and control of haemorrhage, to the exclusion of other priorities. On the surgical side, this concept has led to the development of "damage control" techniques and more aggressive use of angiographic embolization. On the anaesthesia and critical care side, it has led to techniques such as deliberate hypotensive resuscitation and a search for pro-coagulant products.

Most anecdotal experience with FVIIa has occurred in patients with transfusion requirements in excess of 1 blood volume (10 units of RBCs), and at doses similar to those used for initial treatment of haemophiliacs: 80–120 mcg/kg. In the prospective trial of FVIIa in trauma patients mentioned above, the drug was administered at the time of transfusion of the 8th unit of RBC, at a dose of 200 mcg/kg, with repeat doses of 100 mcg/kg 1 and 2 h later.¹ This trial enrolled 280 patients (140 with blunt and 140 with penetrating trauma), and demonstrated a

Table 1 Summary of results: prospective, randomized use of FVIIa in trauma patients¹

	Blunt trauma		Penetrating trauma	
	FVIIa	Placebo	FVIIa	Placebo
<i>n</i>	69	74	70	64
48 h mortality	13	13	12	10
30 day mortality	17	22	17	18
Massive transfusion	8	20	4	10
Death or organ failure	20	31	20	22

There was a statistically significant reduction of 2.0 units of RBC in the first 48 h in blunt trauma patients receiving FVIIa.

reduction in transfusion requirement in those who received FVIIa. Effects were more pronounced in blunt trauma patients than in those with penetrating trauma, although the blunt group was generally more seriously injured, with a higher overall transfusion requirement (Table 1). FVIIa patients had a lower overall incidence of death and organ system failure when these endpoints were combined, and a lower mortality when early deaths (those with predictably fatal haemorrhagic shock at the time of enrollment) were excluded from analysis.

The safety profile of FVIIa in this study was encouraging, with no increase in the incidence of thrombotic complications in the treated patients. More organ system failure was observed in the placebo group, presumably due to their increased transfusion requirement or longer duration of shock. Despite these findings in the prospective controlled trial, there have been a few case reports of thrombotic events associated with off-label FVIIa use in trauma patients, and a few recorded in the case series published to date. However, safety data has been sufficiently persuasive to encourage the US Food and Drug Administration (FDA) to lift the ban on clinical research with FVIIa as of September 2005.

While the use of FVIIa for off-label indications has been growing, it is also clear that FVIIa is a potent agent, and has the potential for producing inappropriate thrombosis in vulnerable patient populations. While there is an obvious bias against reporting major complications in published case reports, other channels have been more active in detailing complications. A recent report from the FDA MedWatch database described 151 thrombotic complications associated with off-label FVIIa use, with the majority of these occurring in trauma patients.¹⁸ A fatal thromboembolic complication (myocardial infarction, pulmonary embolus, ischemic stroke) was associated with FVIIa use in 36 cases. Due to the fact that MedWatch is solely a voluntary listing of observed complications, it is impossible to calculate an incident rate from these data. Additionally, there is insufficient clinical detail to know what the risk/benefit balance was for off-label administration of FVIIa in the cases reported.

In our own institution, clinical experience with FVIIa is now over 250 patients, 150 of these treated for exsanguinating haemorrhagic shock. Our system involves a 'gatekeeper,' defined criteria for use (Table 2), and careful record keeping. Of the patients we treat with FVIIa 85% achieve an immediate correction of coagulopathy, and sustained haemostasis. The remaining 15% are non-responders, suggesting futile administration of the drug. A recent analysis of our data suggests that the degree of haemorrhagic shock at the time of admission to the hospital is the best predictor of futility, as measured by revised trauma score, initial lactate level, and pre-dose prothrombin time.²³ Other large published series have noted the same effect: when given late in the course of disease progression, after massive transfusion is already underway, many patients will not respond.² Pre-clinical laboratory research shows that FVIIa activity is significantly impaired by acidosis, and impaired to a lesser degree by hypothermia.¹⁶ Whether these barriers can be overcome in the patient with acute haemorrhagic shock – say by the administration of bicarbonate to elevate the serum pH – is an open question. While it is relatively easy to establish markers for futility in FVIIa administration (Table 3), it can be hard to rigorously apply these to individual patients *in extremis*, when clinicians are desperately seeking any potentially beneficial therapy.

In our series we have observed six patients with subsequent serious thrombotic complications, consisting of stroke and peripheral arterial occlusion [10]. We have also seen a number of patients develop deep venous thrombosis (DVT) in the days to weeks following FVIIa treatment. Assessment of the causality of these events is complex. These complications occurred in multiple injured trauma patients already at significant risk for complications such as DVT. Additionally, because the complication was typically diagnosed outside of the known 120 min half-life of administered FVIIa, it is difficult to precisely determine the proximate cause of the thrombosis. Based on the literature and our own experience, we do not use FVIIa prior to or during any use of mechanical vascular bypass, and we are extremely cautious when using it in patients with

Table 2 Criteria for "Off-Label" use of FVIIa at the Shock Trauma Center

- 1 **Acuity:** The patient must be in a life-threatening situation
- 2 **Coagulopathy:** The patient must be coagulopathic, either by laboratory evidence (INR) or clinical observation of non-surgical haemorrhage
- 3 **Conventional therapy:** Normal transfusion therapy with plasma and platelets must have failed to resolve the coagulopathy, or be likely to fail in the available time window
- 4 **Futility:** The patient must have a good chance of long-term survival if the coagulopathy can be resolved

All uses must be approved by the physician gatekeeper. Approval is based on the following.

Table 3 Markers for futility in FVIIa administration

Clinical

- Previous cardio-pulmonary resuscitation
- Continuous pressor infusion required to support haemodynamics
- Low revised trauma score at the time of hospital admission
- Potential that the patient has a non-survivable brain injury
- Increased difficulty of the likely surgical repair (multiple injuries, difficult anatomic access)
- Severe hypothermia (core temperature < 33°C)

Laboratory

- Admission prothrombin time abnormal (patients not on warfarin therapy)
- Increased admission lactate
- pH < 7.10 at the time of FVIIa administration

Any of the following variables make it less likely that the haemorrhaging patient will respond to FVIIa. Assessment of futility should be made by an experienced clinician.

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recent arterial anastomoses or stents. Patients with high-energy partial thickness injuries to the carotid, femoral, or mesenteric vessels also appear to be at risk; as vascular imaging studies become more sophisticated it may be possible to prospectively identify the patients at highest risk for a thromboembolic complication.

Evidence from our futility study, and from anecdotal experience, would suggest that giving FVIIa earlier in a haemorrhagic crisis – before native platelets and clotting factors are depleted and before significant tissue acidosis develops – might improve its effectiveness. At the same time, earlier use will expose more and healthier patients to the risk of thrombotic complications. This is the risk–benefit relationship that must be established in future prospective trials. The multicenter trauma trial now underway will use the same (comparatively high) dose as the previous trauma trial, but will start earlier in the disease process (4–8 units of RBC). This trial is designed to examine FVIIa’s utility in patients with documented haemorrhagic shock and the potential for continued further bleeding. Likely targets for future prospective trials include post-cardiac surgery bleeding, bleeding from hepatic surgery or transplant, and bleeding in major orthopedic operations.

Factor VIIa for intracerebral bleeding

One of the most exciting FVIIa developments of the past year was the publication of results from a Phase II multicenter prospective trial in patients with the acute onset of haemorrhagic stroke.¹⁵ Patients were treated with FVIIa or placebo within 3 h of the onset of symptoms. The primary endpoint was the observed degree of haemorrhage expansion from the initial CT scan to one obtained at 24 h. Patients treated with FVIIa had a significant reduction in haemorrhage volume. Since the study was not powered to examine this effect, it was surprising to find

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that FVIIa patients also had improved neurologic outcomes and decreased mortality. This study was also the first prospective trial to demonstrate an increase in the risk of thromboembolic complications following FVIIa administration, although most of the observed events were minor in nature. A Phase III trial is already underway to confirm and expand on these results.

The potential benefit of FVIIa in patients with intraparenchymal haemorrhage from traumatic brain injury (TBI) has not yet been established. These patients are also at risk for haemorrhage expansion in the first 24 h following injury, but a prospective trial of FVIIa therapy in this patient population has not been initiated to date. On the other hand, the use of FVIIa to facilitate emergency neurosurgery is a rapidly expanding off-label use. Pre-procedure use of FVIIa will rapidly normalize prothrombin times in candidates for emergency craniectomy or placement of invasive intracranial or intrathecal monitors. Because of the rich expression of tissue factor in the brain, FVIIa administration, even at doses as low as 10–15 mcg/kg, produces a dramatic reduction in intraoperative haemorrhage, and subjectively improved operating conditions.²¹ Perioperative use of low-dose FVIIa to facilitate neurosurgery – both elective and emergent – has become a relatively common practice in our institution. However, the absence of prospectively collected data means that little is known about the thromboembolic risks of low-dose FVIIa therapy in patients with TBI. The clinician is advised to carefully weigh this risk against the potential benefits to the patient of more timely surgery without large volume administration of plasma.

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Factor VIIa for other uses

Increased experience with FVIIa has led to increased use in trauma patients outside of the narrow focus of

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acute haemorrhagic shock or TBI. The first use in trauma in the United States was actually in an ICU patient several hours removed from the operating room.²⁰ The patient was haemodynamically stable and adequately resuscitated but suffering from a persistent and ongoing coagulopathy. He responded to FVIIa therapy, but died many weeks later of multiple organ system failure and sepsis. Many other case reports document similar "late" use of FVIIa for patients who are not in shock, but are still demonstrating evidence of bleeding and coagulopathy.¹¹ In our own practice, we have used FVIIa to treat patients with ICU coagulopathy secondary to sepsis, cirrhosis, amniotic fluid embolism, and congenital clotting factor abnormalities.⁸ Our experience suggests that most of these patients will normalize after a low dose (1.2 mg) of FVIIa, but long-term outcomes are typically driven by the underlying pathology. The only exception we make to this dosing practice is in patients with active haemorrhage in the setting of severe cirrhosis. In this group, we have begun using a "clotting cocktail" of 100 mcg/kg FVIIa, a pheresis pack of platelets, and 6–10 units of cryoprecipitate. When administered in close proximity, these three agents will work to stop non-surgical bleeding in almost any patient. Nonetheless, long-term outcomes in cirrhotics with serious traumatic injuries remain poor.

Another increasingly common use of FVIIa in our practice is for the rapid reversal of anti-coagulant therapy in patients with new-onset bleeding.³ This scenario is seen often in elderly patients on pre-injury warfarin therapy who present with new intracranial haemorrhage, typically from trivial mechanisms. This type of patient represents a significant therapeutic challenge. The traditional approach of attempting to normalize prothrombin time with Vitamin K and plasma administration before proceeding with neurosurgical interventions will frequently fail, due either to disease progression during the time needed to administer these therapies, or due to fluid overload and cardiac failure as a consequence of the volume administered. We have found that small dose FVIIa will correct the international normalized ratio (INR) in less than 10 min, allowing for immediate surgical intervention. Vitamin K and plasma can then be given over time, to maintain the desired level of coagulation function without the acute risk of volume overload.

Patients who will not accept transfusion, such as Jehovah's Witnesses, represent another challenge for the traumatologist. These patients may benefit from FVIIa. Use of prophylactic doses of the drug (we use 1.2 mg at the time of surgical incision) can substantially reduce intraoperative blood loss and the subsequent need for transfusion in urgently required

abdominal and orthopedic operations.²⁴ Several case reports on this topic have appeared in recent years, reporting that FVIIa therapy is accepted by Jehovah's Witness patients, and appears to be efficacious in reducing intraoperative blood loss.

More generically, the use of FVIIa as a prophylactic therapy to reduce the need for transfusion is an interesting proposition. Freiderich and colleagues demonstrated a significant reduction in intraoperative blood loss and the number of patients requiring transfusion when 20 or 40 mcg/kg of FVIIa were administered at the start of radical prostate surgery.²⁰ Similar prospectively collected data have appeared for elective hepatic surgery,⁴⁴ further suggesting the efficacy of prophylactic administration, although the data from liver transplant operations² and major pelvic surgery²⁴ have been less convincing. Overall, it does seem likely that FVIIa can reduce blood loss from major elective operations. What is less clear is the cost of this therapy; both in financial terms and in the risk of thromboembolic complications. While the latter issue will be clarified by future prospective trials, the expense of FVIIa at this time makes it relatively unpalatable for routine prophylactic use. It is likely that this analysis could change in the coming decades, however, as the long-term risks of transfusion are better defined and as competing pro-coagulant products enter the marketplace.

Uncited references

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