

Management of Severe Peri-operative Coagulopathy: Role of Recombinant Activated Factor VII

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Introduction

Recombinant activated factor VII (rFVIIa) (eptacog alfa, NovoSeven®, Novo Nordisk, Copenhagen, Denmark) was introduced for the treatment of bleeding episodes in FVIII or FIX deficient patients who do not respond to standard replacement therapy, due to the presence of inhibitory antibodies.¹ However, since its introduction, rFVIIa has been used for a wide range of other coagulation disorders, including peri-operative coagulopathies associated with trauma, major surgery and organ transplantation.¹ Initial reports suggest that it is effective in reducing or arresting bleeding in these situations, leading to improvements in patient outcome and conservation of other coagulation products.¹ At the same time, few adverse effects have been reported. This has led to increased requests for peri-operative use of the drug, prompting concerns that it may be used somewhat indiscriminately, despite its high cost (approximately AUS\$6000 per dose). In response, many hospitals have developed guidelines for the peri-operative availability of rFVIIa, restricting its use to those patients who have failed 'conventional treatment' and whose recovery would otherwise be unexpected.

The aim of this paper is to briefly summarise what is considered "conventional treatment" for severe peri-operative coagulopathy, to describe the mechanism of action of rFVIIa, and to discuss its current use and role in the peri-operative period.

Definition of Severe Coagulopathy

A coagulopathy implies that clot formation is impaired. In the most severe coagulopathies, clot formation does not occur. In the surgical setting, a severe coagulopathy is associated with diffuse microvascular bleeding manifesting as persistent ooze from wound edges or vascular anastomotic sites, as well as absence of clot formation in spilled blood. Laboratory features may include severe thrombocytopenia and markedly prolonged coagulation times (e.g. prothrombin time, activated partial thromboplastin time), with or without evidence of fibrinolysis.

Haemostasis vs Coagulation

The terms haemostasis and coagulation are often used interchangeably, which can lead to confusion in the surgical setting. Strictly, haemostasis is the arrest of bleeding through any mechanism, whereas coagulation refers only to the formation of a fibrin clot. Haemostasis can occur in the absence of coagulation (e.g. surgical ligation of a bleeding vessel in a fully heparinised patient). On the other hand, haemostasis may be incomplete despite normal coagulation (e.g. injury to a major blood vessel). Peri-operatively, the situation may fall between these two extremes. For example, a patient may have a coagulopathy, but it may not be clear whether this is the sole cause of bleeding, or whether surgical haemostasis can be improved. In this scenario, attempts should be made to correct the coagulopathy in the first instance. However, if the coagulopathy cannot be corrected in a timely manner or if bleeding is sufficient to cause haemodynamic compromise, surgical intervention is required despite a persistent coagulopathy.

Causes of Peri-operative Coagulopathy

In some circumstances, the cause of a peri-operative coagulopathy is obvious and the treatment can be directed accordingly. However, in many cases, the exact cause is not known, or there is more than one mechanism involved. The causes of most peri-operative coagulopathies fall under one (or more) of the following headings (Table 1):

Table 1
Causes of peri-operative coagulopathy

Drugs	Unfractionated heparin, low molecular weight heparin, heparinoids, direct thrombin inhibitors, warfarin, aspirin, other COX-1 inhibitors, thienopyridines, GpIIb/IIIa inhibitors
Diseases	Pre-existing congenital or acquired deficiencies of platelets or other coagulation factors; liver disease; uraemia
Dilution	Dilution of coagulation factors caused by blood loss and replacement with factor deficient fluids
Destruction	Destruction or reduction of platelet receptors during cardiopulmonary bypass
Drop in temperature	Hypothermia <34°C
DIC	Disseminated intravascular coagulation leading to consumption of coagulation factors and secondary fibrinolysis; also consider primary fibrinolysis

Drugs

Unfractionated heparin is often given during vascular or cardiac surgery. After protamine reversal, some heparin effect may persist due to inadequate dosage or heparin rebound.² Protamine does not fully reverse the anti-Xa effects of low molecular weight heparin or heparinoids.² Even if heparin is fully reversed, excess protamine has anticoagulant effects of its own.^{2,3} Heparin has other effects that inhibit platelet aggregation.^{4,5} In rare instances, heparin may be given inadvertently (e.g. flushing of heparin present in a central venous catheter). Other drugs to consider are oral anticoagulants (i.e. warfarin), antiplatelet agents, and novel direct thrombin inhibitors.^{2,6} Recent ingestion of aspirin or other COX-1 inhibitors alone will not cause a severe coagulopathy, but may complicate other coagulation disturbances.⁶ In contrast, recent clopidogrel may impair platelet function sufficiently to be the primary cause of a coagulopathy.⁶ Glycoprotein IIb/IIIa antagonists such as abciximab are

potent inhibitors of platelet aggregation and increase blood loss if given within a few hours of surgery.⁶ Tirofiban has a shorter half-life than abciximab and is of lesser concern.⁶ Fibrinolytic agents such as streptokinase or tissue plasminogen activator will lyse any clot that is formed, but the effects are short lived.⁷ Direct thrombin inhibitors (eg hirudin, argatroban) may have been used in patients who have recently undergone cardiological interventional procedures.^{2,3}

Diseases

Patients may have a pre-existing coagulation factor deficiency (e.g. factor VIII, factor IX, von Willebrand factor), thrombocytopenia or a platelet function disorder. In emergency situations, this information may not be available. Rarely, the condition may have been previously undiagnosed. Patients with severe liver disease have deficient clotting factor production with varying degrees of thrombocytopenia.⁸ Patients with obstructive jaundice may have ineffective vitamin K dependent factor production (II, VII, IX, X, protein C). Uraemic patients may have impaired platelet function.⁸

Dilution

Patients may develop or exacerbate a coagulopathy peri-operatively if persistent blood loss is replaced with fluids that contain no coagulation factors (or only low levels of them). Platelets in cold-stored whole blood are inactive within a few hours.⁹ The heat labile factors V and VIII become less active in cold-stored whole blood within days. Packed red cells have minimal plasma volume, making them essentially deficient of all coagulation factors. With ongoing blood loss, the decrease in platelet count is the most important defect, although the fall is often less than expected, due to the release of stored platelets from the spleen and other reticulo-endothelial sites.⁹

In any event, abnormal surgical bleeding is unlikely if the platelet count is $>75,000/\mu\text{L}$ (unless platelet function is abnormal). Below a platelet count of $50,000/\mu\text{L}$, abnormal surgical bleeding can be expected. Dilution of coagulation factors rarely impairs coagulation unless their levels fall to $<30\%$ of normal.⁹ This degree of dilution would require blood loss greater than one blood volume.

Severe anaemia itself may contribute to a bleeding tendency.¹⁰ During normal laminar flow, platelets are concentrated peripherally near the vessel wall. Severe anaemia promotes turbulent flow, which mixes platelets throughout the blood flow stream, causing an apparent decrease in platelet count at the vessel wall.

Drop in Temperature

Below 34°C there is progressive impairment of coagulation, particularly if there are other concurrent coagulation disturbances.¹¹ Hypothermia slows the enzymatic reactions involved in coagulation, and the platelet count falls due to sequestration in the liver and spleen. Hypothermia-induced coagulation disturbances appear to self-correct on return to normothermia.

Destruction

Cardiopulmonary bypass (CPB) exposes blood to artificial surfaces leading to activation of coagulation pathways and platelets.¹² Large doses of heparin prevent fibrin formation, but do not prevent the activation of platelets and other coagulation factors. Activated platelets degranulate during CPB, leaving them relatively ineffective

in the post-CPB period. The density of platelet adhesion receptors (e.g. GpIb, GpIIb/IIIa) also falls during CPB, which may result in impaired aggregation subsequently. If fibrinolysis occurs, platelet receptors may be lysed by plasmin. Heparin-bonded circuits (e.g. Carmeda AB, Medtronic Inc, Minneapolis, MN, USA) may reduce activation of coagulation during CPB.³

Disseminated Intravascular Coagulation/Fibrinolysis

Disseminated intravascular coagulation (DIC) may be a complication of severe trauma, septicaemia, fat or amniotic fluid embolism or shock from any cause.⁸ The mechanism involves massive exposure to tissue factor, either through extensive tissue injury or activation of blood components. The result is extensive microthrombi formation, particularly in small vessels, with rapid consumption and depletion of coagulation factors. In response, tissue plasminogen activator is released resulting in a secondary fibrinolysis. This complicates the underlying consumptive coagulopathy. Primary fibrinolysis is less common, but may occur in patients with severe liver disease (eg. during liver transplantation), or during urological surgery, as a result of urokinase release. Activation of fibrinolysis may also occur during prolonged CPB.

Prevention

The development of a peri-operative coagulopathy should be prevented where possible by correction of pre-existing deficiencies, cessation of anticoagulant or anti-thrombotic drugs an appropriate interval pre-operatively, core temperature maintenance $>35^{\circ}\text{C}$ by warming IV fluids and using warm air blankets, and maintaining cardiovascular stability and tissue perfusion by prompt replacement of blood loss (Table 2). During prolonged CPB or deep hypothermic circulatory arrest, activation of coagulation can be minimised by using a Carmeda (or similar) heparin-bonded circuit. In complex cardiac or vascular cases, or major organ transplantation, prophylactic anti-fibrinolytic therapy should be considered (see below).

Table 2
Prevention of peri-operative coagulopathy

Cease	Cease anticoagulant and antiplatelet drugs an appropriate interval pre-operatively
Correct	Correct pre-existing or current deficiencies before they manifest clinically
Core temperature	Maintain core temperature $>34^{\circ}\text{C}$
Cardiovascular stability	Maintain cardiovascular stability and tissue perfusion to avoid shock and release of tissue thromboplastin
Carmeda (or similar) circuit	Consider heparin-bonded circuit during complex cases involving cardiopulmonary bypass

Monitoring

Coagulation tests are of limited use in patients with a severe coagulopathy, particularly if multiple mechanisms are involved.⁹ If there is no evidence of clot formation, most standard coagulation tests are likely to be abnormal. Screening tests such as the prothrombin time (PT) and activated partial thromboplastin time (aPTT) are unable to discriminate between intrinsic and extrinsic pathway defects if there is a severe common pathway defect. Nevertheless, they may provide an index of the severity of a coagulopathy. A heparin effect can be detected by protamine titration against the

aPTT or TCT *ex vivo*. The fibrinogen concentration is useful if DIC or fibrinolysis is suspected.^{8,9} A platelet count provides accurate information about platelet numbers, but not function.

Laboratory tests often involve a long turnaround time, which limits their value in rapidly changing situations. Point of care measurements reduce the delay, but may not be as accurate. Thrombelastography and Sonoclot analysis are useful for mild to moderate coagulopathies, but not for severe coagulopathies when blood remains fluid. The activated clotting time is used for monitoring heparin effect, but is less specific if there are other coagulation disturbances.³ Elevated D-dimer levels confirm fibrinolysis, but this test is rarely available in a timely manner. For the above reasons, it is often necessary to treat severe coagulopathy on an empirical basis.

Conventional Treatment

There are few controlled trials or meta-analyses available to guide management. Most of the available information has been abstracted from studies examining blood loss reduction strategies in elective or semi-elective cases. In any event, there are few therapeutic options. These can be considered under the following headings (Table 3):

Table 3
Treatment of peri-operative coagulopathy

Protamine	Reverse effects of heparin if present
Platelets	Transfuse platelets to maintain platelet count $>75,000/\mu\text{L}$ (where possible); If platelet function is impaired, transfuse platelets irrespective of platelet count
Plasma or plasma fractions	Replace factor deficiencies with plasma or plasma fractions
aProtinin	Use aprotinin or other anti-fibrinolytic drug to reduce or prevent fibrinolysis
ddavP	For mild FVIII or von Willebrand factor deficiency only

Protamine

The only role for protamine in the treatment of a coagulopathy is to reverse the effects of heparin. If there is no heparin present, there is no point in giving protamine. However, if there is heparin present, there is no point in giving anything else until the heparin has been reversed. Therefore, a possible heparin effect should be considered before commencing other treatment. A heparin effect can be confirmed by protamine titration *ex vivo*, either in the laboratory, or at the bedside (e.g. Hepcon HMS, Medtronic, Minneapolis, MN, USA). However, free protamine has an anticoagulant effect and excessive dosage must be avoided.³

Newer agents that are being developed as alternatives to protamine include heparinase and recombinant platelet factor.⁴

Platelets

In the presence of continued bleeding, a platelet count of $>75,000/\mu\text{L}$ should be maintained where possible. Transfusion of platelet concentrates may be necessary.⁹ One unit of platelet concentrate increases the platelet count by $5000\text{--}10,000/\mu\text{L}$ (in a 70 kg adult). If platelet function is impaired (e.g. drugs, destruction of receptors) the platelet count is less relevant, and they should be administered empirically.

The function of allogeneic platelets depends on their duration of storage. As the severity of a coagulopathy increases, the requirement for fresher platelets increases.

However, even fresh platelets will be ineffective if the cause of the platelet dysfunction is still present (e.g. antiplatelet drugs or other inhibitors in the plasma). Ultrafresh whole blood contains the most effective platelets, but is rarely considered, due to its associated risks.¹³

Plasma or Plasma Fractions

Fresh frozen plasma (FFP) contains all the normal coagulation factors and will correct most factor deficiencies irrespective of their cause.^{2,8}

Warfarin effect should be reversed pre-operatively, if possible, by the administration of vitamin K. The amount of FFP required to reverse a warfarin effect can be monitored using the PT. The amount of FFP required to correct a dilutional coagulopathy is more difficult to assess, but should match the number of units of packed red cell equivalents, particularly after the loss of one blood volume. Low levels of fibrinogen, such as occurs with DIC or fibrinolysis may require additional cryoprecipitate, which contains higher concentrations of fibrinogen, factor VIIIc, and vWF.⁹ For patients with known FVIII or FIX deficiencies, highly purified or recombinant specific factor concentrates are available. Recombinant FVIIa is available for FVII deficiencies, and for patients with inhibitory antibodies to FVIII or FIX.¹ Recombinant FVIIa is effective in correcting many other severe coagulopathies (see below).

Aprotinin

If fibrinolysis is present, an anti-fibrinolytic agent such as aprotinin is indicated.¹⁴ Aprotinin is a serine protease inhibitor that forms reversible complexes with trypsin, plasmin, and kallikrein.¹⁴ By binding to plasmin, it inhibits the breakdown of fibrinogen and fibrin. High-dose aprotinin (2 million KIU IV followed by 500,000KIU/hour) inhibits fibrinolysis and reduces peri-operative blood loss in a range of surgical procedures. Its efficacy is reduced at lower doses.

The alternative to aprotinin is epsilon-aminocaproic acid, a synthetic lysine analogue that acts by blocking the active site of plasmin.¹⁴ Epsilon-aminocaproic acid (150 mg/kg IV, followed by 15 mg/kg/hour) significantly reduces blood loss, but appears to be less effective than aprotinin. Tranexamic acid is another synthetic lysine analogue that acts in a similar manner to epsilon-aminocaproic acid.¹⁴ The recommended dose is 10 mg/kg/ IV plus 1 mg/kg/hour IV. Tranexamic acid has fewer side effects, and is cheaper than epsilon-aminocaproic acid, but is not available for IV use in Australia at the present time.

All anti-fibrinolytic drugs theoretically increase the likelihood of thrombosis, although this is less likely in the presence of a severe coagulopathy.¹⁵

DdavP

Desmopressin (1-deamino-8-d-arginine vasopressin), an analogue of arginine vasopressin, temporarily increases the plasma levels of FVIII and vWF.¹⁴ This is achieved by stimulating the release of these factors from endothelial sites. Desmopressin (0.3 mcg/kg over 20 min) is effective for the temporary management of mild cases of haemophilia A, and some types of von Willebrand's disease. There is little or no evidence that it is effective for the reduction of blood loss in other conditions, particularly if FVIII and vWF are being concurrently administered as plasma products.

Packed Cells

Severe anaemia (Hb < 7g/dL) should be avoided by the administration of packed red cells, whole blood or washed autologous cell-saved blood where available. Correction of severe anaemia is required to maintain oxygen delivery, but also promotes laminar flow allowing platelets to concentrate peripherally near endothelial surfaces.¹⁰

Failure of Conventional Treatment

It is difficult to define when conventional treatment of a severe peri-operative coagulopathy has failed, so each hospital should establish its own criteria. For example, one set of criteria could include the loss and replacement of at least one blood volume, with no significant improvement in bleeding or coagulation despite maximal treatment of all treatable causes, for a minimum period of at least 6 hours. The actual criteria will depend on the type of patients treated and the resources available. In any event, once conventional treatment has “failed”, few therapeutic options remain. It may be possible to continue with supportive therapy until the situation either improves, deteriorates, or allogeneic products are exhausted. Another option is the use of ultrafresh allogeneic whole blood from on-site donors. This is usually considered only as a last resort if recovery would be unprecedented otherwise.¹³ Recombinant FVIIa is the new alternative when conventional therapy has failed.¹

Recombinant Activated Factor VII

Mechanism of Action

Factor VIIa has a fundamental role in the initiation of coagulation.^{1, 16} Under normal circumstances, only a small proportion of circulating FVII is in the activated form. Following vascular injury, FVIIa binds to tissue factor (TF) expressed on the membranes of extravascular cells (Figure 1). The TF:VIIa complex activates FIX and FX. Positive feedback occurs when local FVIIa, FIXa, and FXa activate additional FVII. Factor Xa and its co-factor FVa, bind to exposed phospholipid on the membrane of activated platelets. This complex has “prothrombinase” activity, and converts prothrombin to thrombin. Thrombin, in addition to its effects on fibrinogen, activates FV, FVIII, and platelets. The process is rapidly controlled by local inhibitors unless further FXa is produced. Under normal circumstances, the generation of additional FXa by the FIXa:FVIIIa complex is required to sustain thrombin production (Figure 1).

Recombinant VIIa is identical in structure and function to human FVIIa. However, in addition to its TF-dependent activity, rFVIIa has TF-independent activity.¹ Recombinant FVIIa directly activates FX on platelet surfaces in a dose-dependent manner. The concentration of FVIIa required for this effect is much greater than the levels normally present in plasma. The ability to directly activate FX explains how FVIIa promotes prothrombinase production in the absence of FVIIIa and FIXa. The ability to administer rFVIIa in high doses explains its efficacy in a range of situations.

Clinical Experience with rFVIIa

Recombinant VIIa has been approved for the control of bleeding in patients with haemophilia with inhibitors in many countries since 1996.¹ Before that time, it was available as part of a compassionate use programme only. Although it has been approved only for a specific indication, it has been shown to improve coagulation and reduce bleeding complications in a wide range of other conditions. These include

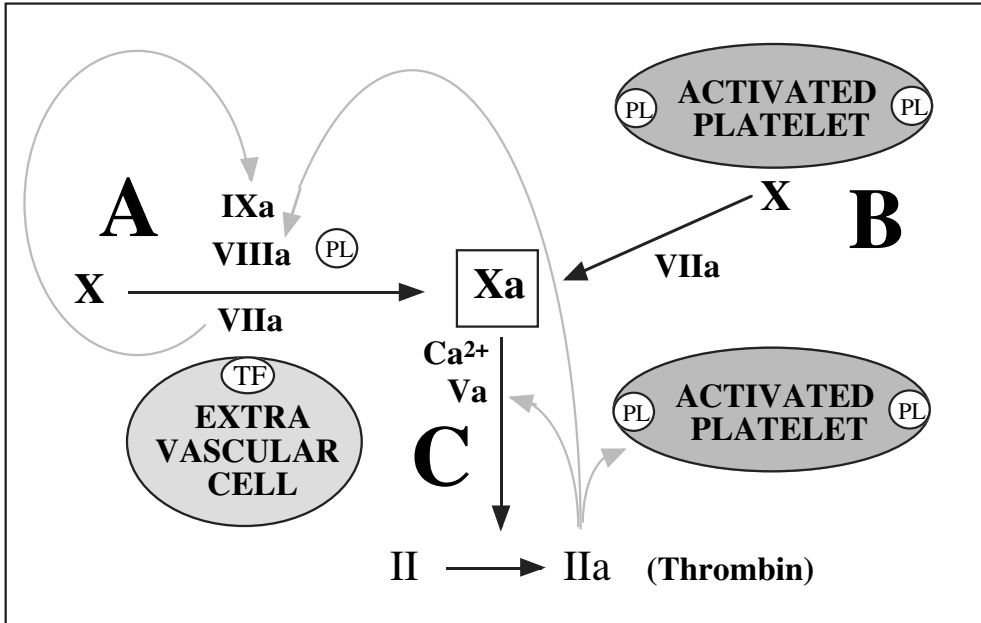


Figure 1. Role of factor VII in coagulation.

- A. Tissue Factor Dependent Pathway.** The small amount of activated FVII in plasma binds to tissue factor (TF) on extra vascular cells exposed at sites of vascular injury. The FVIIa:TF complex activates FX and FIX. The FIXa:FVIIa complex activates further FX, thereby amplifying FXa production.
- B. Tissue Factor Independent Pathway.** High concentrations of FVIIa directly activate FX bound to the surface of activated platelets.
- C. Common Pathway.** Factor Xa with its cofactor, FVa, calcium ions, and platelet phospholipid (PL) converts prothrombin (II) to thrombin (IIa).

thrombocytopenia, warfarin toxicity, liver disease (including fulminant hepatic failure), bleeding in neonates, surgical bleeding and trauma.^{1, 17, 18, 19}

Most of the information on the use of rFVIIa in patients with peri-operative bleeding is in the form of case reports. The first report was by Kenet et al in 1999.²⁰ They described a patient with intractable bleeding due to a gunshot wound. This patient did not respond to maximal conventional therapy, but improved following two doses of rFVIIa, 60 mcg/kg iv. The same group later reported a series of nine trauma patients who failed to respond to maximal transfusion therapy, but who responded to rFVIIa.²¹ None developed clinical signs of thrombosis.

Since 1999, there have been numerous case reports or case series on the efficacy of rFVIIa in surgical patients with severe coagulopathies and intractable bleeding. These have included abdominal surgery,²² urological surgery,²³ orthopaedic surgery,²⁴ cardiac surgery,^{25, 26, 27} obstetric bleeding²⁸ and transplantation.^{29, 30} Initially, most of these cases involved the use of rFVIIa as a last resort in life-threatening bleeding when conventional management had failed. However, the encouraging results have prompted the use of rFVIIa in less severe bleeding. More recent reports suggest that rFVIIa is effective in reducing blood loss in patients with normal coagulation.^{31, 32} Nevertheless, there have been no controlled trials on the efficacy or safety of rFVIIa, other than in patients with haemophilia.

Safety of rFVIIa

No human proteins or blood products are used in the preparation of NovoSeven®.³³ By using recombinant technology, the risk of virus transmission is avoided. Since July 1996 over 250,000 standard doses of rFVIIa have been administered to patients.³³ Few adverse effects have been reported. Non-serious adverse effects that have been attributed to rFVIIa are fever, headache, vomiting and skin hypersensitivity reactions. These are rare and self-limiting. There is no data confirming the safety of rFVIIa in pregnancy.

The incidence of thromboembolic complications is <1%, despite its use in many patients with significant co-morbidities.¹ The low incidence of thrombotic complications may relate to the localisation of rFVIIa effects to sites of vascular injury. Under physiological conditions, rFVIIa requires TF, which is normally present only on extravascular cells. Higher doses of rFVIIa directly activate FX, but only on the surface of activated platelets at sites of vascular injury.

Dosage and Administration

Recombinant FVIIa is available for intravenous bolus use only. It is active within minutes after injection. The half-life of the drug in adults is approximately 2.5h. This is not affected by liver or renal dysfunction. The recommended dose in patients with haemophilia A or B with inhibitors and active surgical bleeding is 100 µg/kg given every 2 hours until haemostasis is achieved.¹ For a 70 kg patient the dose would be 100 µg × 70 = 7.0 mg. In view of the cost per ampoule, it is recommended that the dose is rounded off to the nearest 1.2 mg. A similar dose is recommended for patients with a severe coagulopathy associated with intractable bleeding. In these patients the dose should be repeated every 2-4 hours as necessary.

Cost of rFVIIa

The cost of rFVIIa (NovoSeven®) in Australia is currently AUS\$1050.00 for a 1.2 mg ampoule.³³ A 5 mg ampoule is available at a proportionally higher cost. The approximate cost for a 70 kg patient is AUS\$6000 per dose.

Availability

Recombinant FVIIa was approved for use in haemophilia patients with inhibitors by the Australian Therapeutic Goods Administration (TGA) in late 1998, and has been marketed by NovoSeven® in Australia since that time. It has been available in New Zealand since 1997. Since it is a marketed drug, it is available on prescription by a physician. However, if it is used for indications that do not have TGA approval, the physician must take responsibility for any adverse effects encountered.

NovoSeven® can be purchased through Novo Nordisk Pharmaceuticals (Copenhagen, Denmark). It has a shelf-life of 2 years. Due to its high cost, most hospitals have a protocol for its use, and will not release the drug until certain criteria are met. For peri-operative use, the criteria are usually designed to ensure that rFVIIa is used only for life-threatening situations when conventional treatment of coagulopathy and bleeding have failed. Obtaining the drug usually requires a request at a consultant level, with the involvement of a haematologist.

Current Indications for Peri-operative Use of rFVIIa

At present, the peri-operative use of rFVIIa should be limited to those patients with

severe coagulopathy and life-threatening bleeding who have not responded to maximal conventional therapy and appropriate surgical intervention. Recombinant FVIIa should not be used as a first line treatment for bleeding until its efficacy and safety in the treatment of peri-operative blood loss have been conclusively demonstrated. An exception may be made for patients undergoing procedures with massive blood loss, who do not accept allogeneic blood products for religious reasons. Recombinant FVIIa may be used as a first line treatment only for patients with haemophilia A or B with inhibitors, or for patients with pre-existing FVII deficiency.

Monitoring the Effect of rFVIIa

Although there is a near linear relationship between rFVIIa activity and its plasma level, it is rarely possible to measure rFVIIa activity in the peri-operative period. The recommended dose is based on a target concentration >30 U/mL.³³ Standard laboratory tests are unable to guide therapy.³³ The PT will normalise at about 5 U/mL, well below its peak effect. In contrast the aPTT may not normalise, even with peak therapeutic concentrations. Therefore, monitoring rFVIIa activity is mainly clinical.

The Future

Current and future clinical trials will determine the efficacy, safety and cost-effectiveness of rFVIIa in patients with peri-operative bleeding.³⁴ It is likely that the indications will widen, particularly if there is reduced availability or increased cost of allogeneic blood products. A reduction in the cost of rFVIIa will also influence its use. In the longer term, rFVIIa may be used as an alternative to conventional therapy, rather than as an adjunct. It may also be used for the control of bleeding in non-coagulopathic patients. At present, the relative safety of rFVIIa in coagulopathic patients is of secondary concern, because its use is limited to patients who might not otherwise survive. However, if its use widens, safety issues will be of greater concern. If it fulfils its potential, rFVIIa will be the most significant advance in transfusion medicine for several decades.

References

1. Hedner U, Erhardtsen E. Potential role for rFVIIa in transfusion medicine. *Transfusion* 2002; 42:114-124.
2. Warkenstein TE, Crowther MA. Reversing anticoagulants both old and new. *Can J Anaesth* 2002; 49:S11-S25.
3. Despotis GJ, Joist JH. Anticoagulation and anticoagulation reversal with cardiac surgery involving cardiopulmonary bypass: an update. *J Cardiothor Vasc Anesth* 1999; 13(Suppl 1):18-29.
4. Walker CPR, Royston D. Thrombin generation and its inhibition: a review of the scientific basis and mechanism of action of anticoagulant therapies. *Br J Anaesth* 2002; 88:848-863.
5. Murithi EW, Belcher PR, Day SP et al. Heparin-induced platelet dysfunction and cardiopulmonary bypass. *Ann Thorac Surg* 2000; 69:1827-1832.
6. Samama CM, Bastien O, Forestier F et al. Antiplatelet agents in the peri-operative period: expert recommendations of the French Society of Anesthesiology and Intensive Care (SFAR) 2001 — a summary statement. *Can J Anaesth* 2002; 49:S26-S35.
7. Marder VJ, Sherry S. Thrombolytic therapy: current status. *N Eng J Med* 1988; 318:1512-1520.
8. Martlew VJ. Peri-operative management of patients with coagulation disorders. *Br J Anaesth* 2000; 84:446-455.
9. Miller RD. Transfusion therapy. In: Miller RD, ed. *Anesthesia*, 5th Ed. Churchill Livingstone, Philadelphia, 2000; 1613-1644.
10. Hellem AJ, Borchgrevink CF, Ames SB. The role of red cells in hemostasis: the relationship between hematocrit, bleeding time, and platelet adhesiveness. *Br J Haematol* 1961; 7:42-50.

11. Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology* 2001; 95:531-543.
12. Spiess BD. Maintenance of homeostasis during cardiopulmonary bypass. *J Cardiothor Vasc Anesth* 1999; 13(Suppl 1):2-5.
13. Erber WN, Tan J, Grey D, Lown LA. Use of unrefrigerated fresh whole blood in massive blood transfusion. *Med J Aust* 1996; 165:11-13.
14. Mannucci PM. Drug therapy: hemostatic drugs. *N Eng J Med* 1998; 339:245-253.
15. Levy J. Hemostatic agents and their safety. *J Cardiothor Vasc Anesth* 1999; 13(Suppl 1):6-11.
16. Hoffman M, Monroe DM III. A cell-based model of hemostasis. *Thromb Haemost* 2001; 85:958-965.
17. Kessler C. Haemorrhagic complications of thrombocytopenia and oral anticoagulation: is there a role for recombinant activate factor VII? *Intensive Care Medicine* 2002; 28:S228-S234.
18. Veldman A, Fischer D, Voight B et al. Life-threatening hemorrhage in neonates: management with recombinant factor VII. *Intensive Care Medicine* 2002; 28:1635-1637.
19. Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. *Intensive Care Medicine* 2002; 28:S241-S247.
20. Kenet G, Walden R, Elad A, Martinowitz U. Treatment of traumatic bleeding with recombinant factor VIIa. *Lancet* 1999; 354:1879.
21. Martinowitz U, Kenet G, Segal E et al. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001; 51:431-439.
22. Moscardo F, Perez F, de la Rubia J et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001; 113:174-176.
23. Friederich PW, Geerdink MGF, Spatoro M et al. The effect of the administration of recombinant activated factor VII (NovoSeven®) on perioperative blood loss in patients undergoing transabdominal retropubic prostatectomy: the PROSE study. *Blood Coag Fibrin* 2000; 11(Suppl 1):S129-S132.
24. Tobias JD. Synthetic VIIa to treat dilutional coagulopathy during posterior spinal fusion in two children. *Anesthesiology* 2002; 96:1522-1525.
25. Hendriks HG, van der Maaten, de Wolf J et al. An effective treatment of severe intractable bleeding after valve repair by one single dose of activated recombinant factor VII. *Anesth Analg* 2001; 93:287-289.
26. Al Douri M, Shafi T, Al Khudairi E et al. Effect of the administration of recombinant activated factor VII (rFVIIa, NovoSeven®) in the management of severe uncontrolled bleeding in patients undergoing heart valve replacement surgery. *Blood Coag Fibrin* 2000; 11(Suppl 1):S121-S127.
27. Von Heymann C, Hotz H, Konertz W, Kox WJ, Spies C. Successful treatment of refractory bleeding with recombinant factor VIIa after redo coronary artery bypass graft surgery. *J Cardiothor Vasc Anesth* 2002; 16:615-616.
28. Breborowicz GH, Sobieszcyk S, Szymankiewicz M. Efficacy of recombinant activated factor VII (rFVIIa, NovoSeven®) in prenatal medicine. *Arch Prenatal Med* 2002; 8:21-27.
29. Kallcinski P, Kaminski A, Drewniak H et al. Quick correction of hemostasis in two patients with fulminant liver failure undergoing liver transplantation by recombinant activated factor VII. *Transplantation Proceedings* 1999; 31:375-379.
30. Shami VM, Caldwell SH, Hespeneheide EE. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. *Liver Transplantation* 2003; 9:138-143.
31. O'Neill PA, Bluth M, Gloster ES et al. Successful use of recombinant activated factor VII for trauma-associated hemorrhage in a patient without a pre-existing coagulopathy. *J Trauma* 2002; 52:400-405.
32. Mayer SA. Intracerebral hemorrhage: natural history and rationale of ultra-early hemostatic therapy. *Intensive Care Medicine* 2002; 28:S235-S240.
33. Product information. Novo Nordisk Pharmaceuticals, Copenhagen, Denmark.
34. Erhardtsen E. Ongoing NovoSeven® trials. *Intensive Care Medicine* 2002;28:S248-S255.