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RECOMBINANT FACTOR VIIA IN NONHAEMOPHILIAC CONDITIONS

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Please see the NSW TAG website for more information.
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Key Messages

Recombinant Factor VIIa (rFVIIa) is indicated in Australia for the control of bleeding and surgery prophylaxis in patients with inhibitors to coagulation factors FVIII or FIX. In addition this drug has orphan status for therapy of bleeding in FVII deficiency, inherited platelet disorders, and post-partum haemorrhage unresponsive to standard obstetric management. Other uses of rFVIIa are considered “off-label”. The uncertainties regarding the prophylactic and therapeutic off-label use of rFVIIa are the subject of this position statement.

The following recommendations are made about the off-label use of rFVIIa in specific indications, based on the level of currently available evidence. A positive recommendation (Grades A or B) is made if there are systematic reviews of randomised controlled trials (RCTs, level I or level II) to support the use of rFVIIa for a particular condition. A qualified recommendation (Grade C) is made if there are nonrandomised or other studies (level III) with some consistency of benefit. Therapy is not recommended if the evidence base consists of case studies, case series or other studies with high risk of bias or inconsistent results (Grade D) or if there are studies showing lack of efficacy.

Overall the evidence base for use of rFVIIa as a therapeutic agent, particularly for intracerebral haemorrhage (ICH), is better than for its prophylactic use. Thus, rFVIIa should not be used prophylactically and has a limited role therapeutically, as per the recommendations below. Further results from ongoing RCTs are required before any further recommendations may be made.

Unless otherwise specified, recommendations relate to adult patients only. The evidence base to support use in the paediatric population is even more limited (see Paediatrics recommendation below and pages 33-37)

Place in Therapy

Initial surgical and/or medical management of life-threatening bleeding should be undertaken according to a clearly defined protocol that includes the following:

- Identification and correction of any reversible defect (such as hypothermia and acidosis)
- Surgical intervention or embolism if required
- Appropriate transfusion of blood components (ie, packed red blood cells [RBCs], fresh frozen plasma [FFP], platelets, cryoprecipitate). In the case of paediatric patients, specialist paediatric haematology advice should be sought
- Reversal of the anticoagulant effects of heparin (protamine sulphate)
- Reversal of the anticoagulant effects of warfarin (prothrombinex-HT and vitamin K)
- Administration of pharmacological agents (eg, aprotinin and fibrinolytic inhibitors)

- Regular monitoring of FBC, PT, APTT, fibrinogen and D-dimer.

In patients with continued life-threatening bleeding despite appropriate conventional surgical and/or medical treatment to control bleeding, rFVIIa may be considered as additional therapy. The amelioration of coagulopathy thrombocytopenia (target platelets $>50,000 \times 10^9/L$), coagulopathy (target fibrinogen $>1.0 \text{ g/L}$), acidosis (pH >7.2) anaemia (haematocrit $>24\%$), and hypothermia are desirable for rFVIIa to be effective.

Positive recommendations (Grade A or B evidence)

- ICH: It is reasonable to consider use of rFVIIa in the management of ICH in adults if it can be given within 4 hours of symptom onset. It should be noted, however, that this recommendation is based on a single RCT in comparison with placebo and efficacy in comparison with other therapies has not been tested. At this point in time, use should only be considered where standard therapy is not a reasonable option and ideally as part of a clinical trial. Concern exists regarding thromboembolic complications at dosages beyond $80 \mu\text{g/kg}$. Use with caution in patients with risk factors for thromboembolic disease.

Qualified recommendations (Grade C evidence)

- Liver surgery: rFVIIa may be of benefit for patients with unexpected life-threatening bleeding when given as additional therapy to surgical and/or medical control of bleeding.
- Cardiac surgery: rFVIIa may be of benefit for patients with life-threatening bleeding as additional therapy to surgical and/or medical therapy to control bleeding. Use of rFVIIa has also been shown in small RCTs to reduce need for transfusion when given after cardiac bypass to prevent bleeding. However, results of prospective comparative studies are required to guide definitive recommendations, including dosage. Use in this indication should only be considered as part of a clinical trial and when other therapies have failed.
- Other surgery: rFVIIa may be of benefit for patients with unexpected life-threatening bleeding as additional therapy to surgical and/or medical control of bleeding. Use should only be considered as part of a clinical trial and when other therapies have failed.
- Blunt trauma: rFVIIa may be of benefit for patients with life-threatening bleeding in the context of blunt trauma. Uncertainty exists regarding recommended dosage. Use should only be considered as part of a clinical trial and when other therapies have failed.
- Reversal of warfarin: while rFVIIa would be expected to partially reverse the effect of warfarin, other effective therapies which correct all warfarin-induced factor deficiencies are available. Off-label use of rFVIIa for reversal of warfarin should only be considered in the context of ICH (see above).

Not recommended (Grade D evidence)

- Other surgery: Prophylactic use of rFVIIa in elective surgery cannot be recommended.
- Penetrating trauma: Results for benefit of rFVIIa in penetrating trauma are conflicting. Surgical control of massive haemorrhage is the first line of management as rFVIIa appears less effective when very high RBC transfusion rates are required. rFVIIa may be of benefit for patients with life-threatening bleeding as additional therapy to surgical and/or medical correction of bleeding, however conflicting results have been reported.
- Reversal of other anticoagulants: While of potential benefit, there is insufficient evidence for a primary role of rFVIIa in reversal of anticoagulation with heparin-like molecules and novel anticoagulant agents.
- Paediatrics: The evidence base for using rFVIIa in children is very limited. There are recognised difficulties in conducting appropriate studies to obtain good evidence in paediatrics as well as uncertainties regarding dosing. The only published RCT in the paediatric population (cardiac surgery for congenital heart disease) showed no benefit of rFVIIa prophylaxis and possibly harm, with significantly prolonged time to chest closure in the rFVIIa treated group. rFVIIa maybe of benefit for paediatric patients with life-threatening bleeding in the context of trauma, surgery, liver disease and prematurity when used as additional therapy to surgical and/or medical control of bleeding. However, its use is not recommended in patient populations where there is a risk of thromboembolism (eg trauma, congenital heart disease, other hyperviscous or hypercoagulable states, presence of arterial or central venous catheters).

Not recommended (Grade A or B evidence that rFVIIa is ineffective)

- Cirrhosis (eg, oesophageal variceal bleeding): rFVIIa should not be used for variceal and non-variceal haemorrhage in patients with cirrhosis (Grade B).
- Liver surgery: Prophylactic administration of rFVIIa is not effective during orthotopic liver transplantation or liver resection (Grade B).

Patient selection and predicting response

A recommendation about which patients will likely benefit from rFVIIa treatment is not currently possible.

A universally beneficial effect of rFVIIa in nonhaemophiliac conditions may not be expected, not only because of the wide variation in bleeding conditions but also because of patient characteristics. Administration of rFVIIa may stem bleeding in some patients but they still die of shock or re-bleeding.

General considerations

The patient or their next of kin should be advised of the proposed risks and benefits of off-label use of rFVIIa. Hospitals should devise a system of review and analysis of all cases of off-label rFVIIa usage.¹

Safety

There are conflicting results regarding the thromboembolic risk of rFVIIa. Uncertainty exists regarding the magnitude of this risk and possible predisposing factors for thromboembolism to guide clinicians in patient selection. Patients and their families should be aware of this potential complication, especially in cases of off-label usage. Well designed prospective studies are required to address this important issue.

Dose

A dosage range of 41 to 90 µg/kg of rFVIIa for all off-label uses has been used (although higher doses have been used in some studies). The published literature does not provide information to determine whether there is a dose response relationship for these off-label uses, although some studies suggest that the risk of thromboembolic adverse events may be increased at higher doses.

Cost considerations

Adequate data to assess cost effectiveness for rFVIIa does not exist for most off-label indications.

Introduction

Haemostasis *in vivo* is predominantly directed by factor VIIa (FVIIa). FVIIa in combination with tissue factor exposed at sites of tissue injury activates plasma factor X and drives thrombin generation. Thrombin is the key enzyme that converts fibrinogen to fibrin, activates platelets, and forms a stable haemostatic plug. Recombinant factor VIIa (rFVIIa, eptacog alpha activated, NovoSeven) is a new therapeutic agent administered by intravenous injection with identical activity to native FVIIa. This agent has revolutionised the management of bleeding in patients with congenital or acquired haemophilia and inhibiting antibodies toward factor VIII or IX. This is the current registered indication for use of this agent. The potential of this haemostatic agent to control serious bleeding in nonhaemophiliac patients has been reported. Increasingly rFVIIa is being prescribed for a variety of “off-label” indications.

Objective of review

This review collates the available evidence on the efficacy and safety of rFVIIa in various clinical situations. It supersedes a previous report compiled in October 2002 by NSW TAG where the recommendation, based on data at that time, was that rFVIIa be used as “rescue” therapy for massively transfused patients with persistent bleeding despite appropriate blood component transfusion, haemostatic measures, pharmacological measures and surgical intervention.² The purpose of this review is to update this information and provide NSW hospital drug committees with recommendations on off-label use of rFVIIa.

Methodology

A focused search of Embase (January 2002-2007 week 9) using the MESH terms “blood clotting factor 7” or “blood clotting factor 7a” or “recombinant blood clotting factor 7a” (2438 results) was performed (limited to human studies and treatment with 2 or more terms high sensitivity and articles [277 results] or reviews[112]). The same search was performed limited to case control studies/cohort analyses (11 results). All of the results were assessed, and the selected papers are presented in this document. A similar Medline search provided no more relevant results. Searches of Best Evidence (AJP Journal Club, EBM), Cochrane, CADTH, Medscape, NICE, SIGN, Guideline Clearing House, MJA and NHMRC were also performed – useful material was obtained from CADTH and Medscape only. Protocols/guidelines from Australian hospitals were solicited and a reference list and further published guideline documents were obtained from Novo Nordisk. The Haemostasis Registry provided their latest results.

This document is not a systematic review or the consensus of key opinion leaders. Rather, it is a review of published evidence based on the levels of evidence and grades developed by the NHMRC pilot program (2005-2007). Positive recommendations (Grades A or B) were made if there were systematic reviews of randomised controlled trials (RCTs, level I) or RCTs (level II) to support the use of rFVIIa for a particular condition. A qualified recommendation (Grade C) was made if there were only nonrandomised or other studies (level III) with some consistency of benefit. A Grade D recommendation was made if the evidence base consisted of case studies, case series or other studies with high risk of bias. The NHMRC grading system is efficacy focussed. Readers should also consult the safety section of this paper when assessing the risk-benefit ratio of drug therapy.

The extent of published material is, of course, different for each condition. Readers should pay most attention to systematic reviews and RCTs. For some conditions, such reviews and RCTs are scant or absent but weaker evidence from other studies and cases has been included - this evidence is subject to considerable publication bias. The extent of reporting of such material in each section does not signify any recommendation by NSW TAG but is given as a sample (ie, not exhaustive) of the body of evidence. Relevant unpublished information, especially regarding safety outcomes, has also been collated from several sources (eg ADRAC, FDA, and the Haemostasis registry).

The use of rFVIIa in patients with Glanzmann's Thrombasthenia (GT) or in the treatment of postpartum haemorrhage has not been included as it has been designated orphan drug status for these indications by the Therapeutic Goods Administration (TGA, see next section).

Product Profile

rFVIIa is indicated in Australia for the control of bleeding and surgery prophylaxis in patients with inhibitors to coagulation factors FVIII or FIX. The TGA designates rFVIIa as an orphan drug for the prevention and treatment of bleeding episodes in patients with congenital Factor VII deficiency or GT (date of designation 14 January 2005). It is also an orphan drug for the treatment of postpartum haemorrhage in patients unresponsive to standard obstetrical management, oxytocic drugs and standard blood component therapy prior to major invasive therapy (date of designation 30 January 2007).

It is available as NovoSeven from Novo Nordisk as a powder for reconstitution containing rFVIIa 0.6 mg/ml when reconstituted with water for injections. It is administered by bolus injection over 2 to 5 mins in order to achieve high peak plasma concentration. Dosages for bleeding control are 35 to 120 µg/kg every 2 to 3 hours till control then every 3 to 12 hours, if needed. Prophylactic dosage is 35 to 120 µg/kg every 2 to 3 hours for 1 to 2 days then every 2 to 6 hours if needed. Pack sizes are 1.2, 2.4 and 4.8 mg vials.

The risk of a potential interaction between NovoSeven and coagulation factor concentrates is unknown and caution is advised if they are used simultaneously. Concomitant use of antifibrinolytic therapy (tranexamic acid, aminocaproic acid) in minor and major surgery is clinically safe and not associated with an increased risk of thrombotic complications or laboratory evidence of consumption coagulopathy though there are recent reports of an increased risk of long-term mortality in coronary artery bypass graft patients who received aprotinin.³⁻⁶

Current price of NovoSeven (2006-7 financial year) is \$1238.46 per 1.2mg vial, \$2476.92 per 2.4mg vial and \$4953.84 per 4.8mg vial (all GST exclusive prices, personal communication Novo Nordisk).

Guidelines and Systematic Reviews

Systematic reviews

Few RCTs on the use of rFVIIa in nonhaemophiliac conditions have been published but several trials are ongoing (see table 1). Several authors have attempted to review the literature systematically.

Table 1. Ongoing rFVIIa studies(Vincent, Rossaint et al. 2006)

Indication	Phase	Description
Traumatic injury	3	Multicentre, double-blind, randomised, parallel-group, placebo-controlled study. Treatment of refractory bleeding in trauma patients
Upper Gastrointestinal bleeding	2	Multicentre, double-blind, randomised, parallel-group, placebo-controlled study. Safety and efficacy in treatment of variceal bleeding in patients with cirrhosis
Cardiac surgery	2	Multicentre, double-blind, randomised, parallel-group, placebo-controlled dose-escalation study. Safety and efficacy in treatment of postoperative bleeding following cardiac surgery in patients requiring cardiopulmonary bypass
Cardiac surgery	3	Randomised, double-blind, placebo-controlled, parallel-group study. Safety and efficacy in salvage use following inadequate haemostatic response to conventional therapy in complex cardiac surgery
Surgery	2	Multicentre, double-blind, randomised, parallel-group, placebo-controlled comparison of rFVIIa and standard haemostatic replacement therapy following cardiac bypass surgery for paediatric congenital heart disease

The most recent systematic review was published by the Cochrane Collaboration (Stanworth et al 2007). They included 13 RCTs in their evaluation (all of these are included in this Position Statement) - 6 involving prophylactic use of rFVIIa (724 patients) and 7 of therapeutic use in 1214 patients. Pooled results from the prophylactic studies showed no significant advantage (or disadvantage in the case of adverse events) of rFVIIa over placebo; however, the authors stated there was a trend towards reduced transfusion requirements with rFVIIa compared with placebo but an increased trend in thromboembolic adverse events. Similarly, no significant advantage or disadvantage was found from pooled results of the therapeutic trials but a trend for reduced mortality and increased risk of thromboembolic adverse events with rFVIIa was found. Note however, they did not include the RCT in intracranial haemorrhage (ICH) in their pooled results because of methodological differences from the other studies – this study did show a positive result for rFVIIa use in ICH. The authors concluded that the use of rFVIIa either prophylactically or therapeutically in nonhaemophiliac patients remains uncertain. They

argue that current results are more positive for therapeutic than prophylactic use of rFVIIa and that future research should give priority towards therapeutic use, with mortality as a primary outcome, or, if blood loss/transfusion requirements are being measured, these trials should be adequately powered (ie, the magnitude of rFVIIa treatment effect has been smaller than hoped for in published trials).

The conclusion of a systematic review of studies up to July 2004 was that rFVIIa is a promising prohaemostatic agent in nonhaemophiliac patients who suffer from major bleeding.⁷ The authors recommended that off-label use may be considered in patients with life-threatening bleeding but that more RCTs are required to assess its efficacy and safety.

In one study, a US consensus panel made recommendations based on grading of published evidence (data up to June 2004) and use of rFVIIa in different clinical scenarios.⁸ In summary, rFVIIa in nonhaemophiliac conditions was deemed appropriate as follows:

- cardiac, thoracic aortic, or spinal surgery; hepatic resection; hysterectomy; or postpartum bleeding (when significant clotting factor replacement has failed)
- for severe multiple trauma (only if surgery and substantial blood replacement are unsuccessful)
- for non-traumatic intracranial bleeding (only if less than 4 hours has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and haematoma expansion).

The Canadian Agency for Drugs and Technologies in Health (CADTH) published a review of 11 double-blind, RCTs of rFVIIa in nonhaemophiliac conditions.⁹ All of these studies are reported in this Position Statement. From all of the studies, there were 2 significant results for rFVIIa compared with placebo:

- rFVIIa showed a significant reduction in mortality among patients with ICH.¹⁰
- rFVIIa reduced the number of trauma patients needing massive blood transfusion.¹¹
- There was a non-significant trend towards increased mortality and thromboembolic serious adverse events in some trials (eg, liver transplant, upper GI bleeding, stem cell transplantation).

The authors stated that the efficacy and safety of rFVIIa in nonhaemophiliac conditions will only become clear after adequately powered Phase 3 trials are published, and that implementation also requires more evidence on its benefit/harm, optimum dose, time of administration, and cost effectiveness.

Most recently, European consensus guidelines based on a systematic review of literature published up to July 2005 are available, which state that rFVIIa may be used to treat massive bleeding in certain indications; however, only in addition to the surgical control of bleeding once conventional therapies have failed.¹² The authors used best evidence to make graded recommendations (A to E) and stated that the following conditions may be treated with rFVIIa:

- control of bleeding in blunt trauma (B – supported by 1 large RCT)

- bleeding following cardiac surgery (D – supported by at least one nonrandomised study)
- postpartum haemorrhage (E – supported by sufficient case series, uncontrolled studies and expert opinion)
- uncontrolled bleeding in surgical patients (E).

It was not recommended for use in management of massive haemorrhage associated with penetrating trauma, elective surgery, liver surgery, or bleeding due to Child-Pugh A, B or C cirrhosis.

Clinical experience and registry information

There are no published Australia-wide guidelines for the unlabelled use of rFVIIa. A similar situation exists in other countries and the reason given is the lack of RCTs to provide evidence-based guidelines. This has prompted the development of guidelines by multidisciplinary working groups, based on clinical experience with the drug. In one US institution, guidelines were implemented as a result of evaluation of medication use.¹³ They produced guidelines for use of rFVIIa in reversal of warfarin toxicity, liver disease, intracerebral haemorrhage (ICH), and in paediatrics. Similarly, a multidisciplinary task force in Israel produced guidelines for the use of rFVIIa in uncontrolled bleeding.¹⁴

Similar approaches to guidelines development have been conducted in several Australian hospitals. Supporting references and the review process were stated in some guidelines though methodology was not given.¹⁵⁻¹⁹ The various Australian hospital guidelines agree that rFVIIa may be useful in cases of life-threatening haemorrhage, providing conventional measures are taken to correct bleeding before rFVIIa is recommended by specialist staff. A consensus recommendation on the use of rFVIIa in cardiac surgery is available from Novo Nordisk (see cardiac surgery section below).²⁰

Registry information

Registries for rFVIIa use in off-label conditions provide valuable information to complement data obtained from RCTs and other published and unpublished sources of evidence; however, their results can only be used as guidance and no firm recommendations may be made from them. Voluntary submission of cases (eg, Haemostasis.com) makes them subject to more bias.

The Haemostasis Registry was established by the department of Epidemiology at Monash University to collect data on the use of rFVIIa in nonhaemophilic patients in Australia and New Zealand with critical bleeding (<http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html>). It is supported by an unrestricted educational grant from NovoNordisk and is coordinated by an expert panel of specialists including haematologists and anaesthesiologists. The purpose of this registry is to “gain information on safety, efficacy and appropriateness of use and dosages of recombinant activated factor VII (rFVIIa, NovoSeven) where it is used for non-haemophilic patients. Establishment of a register will provide valuable observational data including efficacy, adverse events, effective dosage and cost-effectiveness. This data will be of substantial value in the development of prospective

trials.” Workshop presentations available on their website show that, as of April 2007, there have been 1205 cases from 70 participating hospitals. Reports from the first 1127 cases show that cardiac surgery is the largest area of use (43% of cases) followed by other surgery (19%) then trauma (14%). Results to date and analyses are presented in Powerpoint but these have not yet been published in any journals (see pages 40, 42-43 for reporting of some interesting outcome data from this registry).

Another NovoNordisk-sponsored database on extended-use rFVIIa was begun in 2001 and collates details from voluntary submissions of off-label use of rFVIIa (Haemostasis.com). An initial report of 40 patients showed some efficacy in stopping bleeding and reducing blood product use.²¹ Twenty three of 40 patients died (16 non-bleeding deaths). A further selective analysis of this registry of 45 surgical and trauma patients (February 1999 to February 2004) suggested that rFVIIa may reduce mortality rate in trauma patients, but this was not observed among the small cohort of surgical patients.²² A review of 24 cases submitted to the same database suggests that rFVIIa is beneficial in the management of haemorrhage in patients with thrombocytopenia and haematological malignancies.²³

Liver Disease

Overall recommendations

Level of evidence

There is one RCT in patients with cirrhosis which showed no benefit of rFVIIa in variceal and non-variceal haemorrhage.²⁴ Case series have found inconsistent benefit. In the systematic review section see page 12-14), rFVIIa is not recommended for use in bleeding due to Child-Pugh A, B or C cirrhosis.¹²

Recommendation

Grade B: rFVIIa cannot be recommended for variceal and non-variceal haemorrhage in patients with cirrhosis.

Reviews

There is one RCT in patients with cirrhosis which showed no benefit of rFVIIa in variceal and non-variceal haemorrhage.²⁴ Case series have found inconsistent benefit. In one systematic review, rFVIIa was not recommended for use in bleeding due to Child-Pugh A, B or C cirrhosis.¹²

RCTs

The efficacy and safety of rFVIIa in 245 cirrhotic patients with variceal and non-variceal upper gastrointestinal (GI) tract bleeding was investigated in a RCT.²⁴ Patients received 8 doses of 100 µg/kg rFVIIa or placebo (as well as other pharmacological and endoscopic treatment). There was no advantage of rFVIIa over standard treatment on the primary composite endpoint (failure to control bleeding within 24 hours after first dose, or failure to prevent re-bleeding between 24 hours and day 5, or death within 5 days), and no significant differences were observed in mortality. However, sub-group analysis of Child-Pugh B and C cirrhotic patients showed that administration of rFVIIa may decrease the proportion of patients who have failed to control variceal bleeding.

Other studies and cases

There is one dose-escalation study of rFVIIa in Child's B and C cirrhotic, non-bleeding patients with advanced liver disease.²⁵ Ten patients with abnormal prothrombin time (PT) values were given 3 successive dosages of rFVIIa (5, 20, and 80 µg/kg) over a 3-week period. The mean PT was transiently corrected to normal in all 3 dose groups. This result cannot be extrapolated to bleeding patients.

A retrospective analysis of 55 patients who received rFVIIa at one institution looked at mortality and outcome.²⁶ Underlying liver disease with coagulopathy was the reason for giving rFVIIa in 26 of the patients. Administration of rFVIIa corrected laboratory

parameters of coagulopathy, but did not alter outcome and 26 patients died during the same admission from their underlying diseases.

The remaining articles are all case series or case studies. For example, in one series of 112 patients with cirrhosis and an episode of acute upper GI bleeding there were 8 who experienced haemorrhage unresponsive to standard treatments. rFVIIa (4.8mg single IV dose) achieved haemostasis in all cases.²⁷ There is a report of 4 cases with advanced cirrhosis and severe coagulopathy that underwent polypectomies by snare cautery after an intravenous bolus infusion of 120 µg/kg rFVIIa.²⁸ The immediate use of rFVIIa reduced resource utilization and enabled polypectomies at the initial colonoscopy. No postpolypectomy bleeding was noted.

Liver surgery

Overall Recommendations

Level of evidence

Case series suggest the potential of benefit; however, 2 RCTs in orthotopic liver transplant (OLT) and 2 in liver surgery consistently found no significant benefit of prophylactic rFVIIa over placebo.²⁹⁻³² In the systematic review section on pages 12-14, all of these studies with the exception of Shao et al are cited in the papers and the following recommendations are made:

- rFVIIa is recommended in hepatic resection or OLT when significant clotting factor replacement has failed.⁸
- rFVIIa is not recommended for prophylactic use in liver surgery but may be used in surgical bleeding if conventional measures have failed.¹²

Recommendations

Grade C: rFVIIa may be of benefit for patients with unexpected life-threatening bleeding as additional therapy to surgical and/or medical control of bleeding.

Grade B: prophylactic administration of rFVIIa is not effective during OLT or liver resection.

Reviews

A literature review in major abdominal and liver transplantation surgery (details of search not given) concluded there is no evidence to support extensive use of rFVIIa in liver transplantation; however, it may be effective as a rescue therapy in extremely severe situations.³³

RCTs

There are 2 RCTs of the prophylactic use of rFVIIa in cirrhotic patients (Child-Pugh class B or C) undergoing OLT.^{29, 31}

In one study, 82 patients were randomised to receive a single dose of rFVIIa (20, 40, or 80 µg/kg) or placebo administered immediately before surgery.³¹ There were no significant differences in the primary endpoint (number of red blood cell [RBC] units required) compared with placebo and the number of adverse events was comparable among the groups. The authors suggested that the doses used might be too low. In a subsequent study in 183 patients, higher rFVIIa doses (60 and 120 µg/kg) or placebo were repeated every 2 hours perioperatively.²⁹ However, this study also showed no significant effect of rFVIIa over placebo on the number of RBC units transfused (primary endpoint, 15% and 23% respective reductions compared with placebo) or intraoperative blood loss. A greater number of patients who received rFVIIa avoided RBC transfusion (8.3% placebo vs 0% rFVIIa, p=0.03). Administration of rFVIIa but not placebo restored

the PT to normal during surgery. There were no group differences in rate of thromboembolic events, hospitalization rate, total surgery time, and the proportion of patients undergoing retransplantation.

An RCT in 204 non-cirrhotic patients undergoing liver resection showed that rFVIIa (20 or 80 µg/kg, 5 minutes before the first skin cut) produced no significant reduction in RBC requirements (primary endpoint), blood loss, or the number of patients transfused.³⁰ The authors suggested the study population was too small to detect a significant difference. The use of rFVIIa (50 or 100 µg/kg) or placebo was investigated in 234 cirrhotic patients undergoing liver resection.³² Active drug or placebo was given 10 minutes before the first skin cut and 2-hourly during surgery. Blood loss was used as a transfusion trigger and the requirement for RBC transfusion was the primary endpoint. There was no statistical difference among the groups.

Other studies and cases

A retrospective study found that prophylactic rFVIIa (58±18 µg/kg) reduced transfusion requirements in 11 OLT patients with high model of end-stage disease (MELD) scores and significantly prolonged PT.³⁴ In a report of 4 cases of fulminant hepatic failure undergoing urgent OLT, the prolonged PT was corrected by rFVIIa (90 µg/kg before and during surgery) in all patients; however, thrombotic complications occurred in 2 patients (myocardial ischaemia, portal vein thrombosis).³⁵ Recombinant FVIIa (60-90 µg/kg) was administered to 7 patients undergoing OLT, 6 of whom experienced persistent severe bleeding and were given rFVIIa (after conventional measures had failed to stop bleeding) during surgery.³⁶ In all cases, rFVIIa allowed sufficient haemostasis to carry on definitive treatment, and there were no deaths.

Surgery and trauma

Cardiac surgery

Overall recommendations

Level of evidence

There is a small RCT in cardiac surgery that showed prophylactic rFVIIa reduced the need for transfusion. Another small RCT showed that rFVIIa can effectively improve coagulation function in patients receiving cardiac valve replacement under cardiopulmonary bypass and reduce the need for blood transfusion. A systematic review recommended the use of rFVIIa, based on this RCT as well as 9 uncontrolled studies that showed consistent benefit from rFVIIa given after surgery and conventional measures of blood cessation. The more recent nonrandomised papers summarised below all show similar benefit. Furthermore, consensus guidelines developed by Australian clinicians (available from Novo Nordisk) state that rFVIIa should be used when all other measures have failed to stop bleeding in cardiac surgery.²⁰ In the systematic review section on pages 12-14, the following recommendations were made:

- rFVIIa was deemed appropriate in cardiac surgery when significant clotting factor replacement had failed.⁸
- rFVIIa may be used to control bleeding following cardiac surgery (though lack of RCTs to support this was noted).¹²

Recommendation

Grade C: rFVIIa may be of benefit for patients with life-threatening bleeding as additional therapy to surgical and/or medical correction of bleeding. Use of rFVIIa has also been shown in a small RCT to reduce need for transfusion when given post cardiac bypass to prevent bleeding. Results of prospective comparative studies are required to guide definitive recommendations, including dosage.

Reviews

There is a recent systematic review of the usefulness of rFVIIa for intractable bleeding after cardiac surgery.³⁷ Ten studies were found (over the period 2000 – 2006), 9 of which were uncontrolled studies in small numbers of patients (range 5 – 51 patients). The only RCT (see below) is in 20 patients where rFVIIa was given prophylactically. The authors summarised the results of all studies and stated that rFVIIa (60-90 µg/kg) produced consistent reductions in blood loss and use of blood products. They recommend its use. A more recent systematic review in cardiac surgery concludes that although definitive evidence from RCTs is lacking, the use of rFVIIa in refractory postoperative haemorrhage is promising but requires much more research.³⁸

RCTs

In a pilot RCT, rFVIIa was given after cardiopulmonary bypass to prevent bleeding.³⁹ Twenty patients received rFVIIa (90 µg/kg) or placebo after cardiopulmonary bypass and reversal of heparin. The study was underpowered but the authors stated that rFVIIa significantly reduced the need for allogeneic transfusion (2 rFVIIa patients received 13 units of blood in total while 8 placebo patients required 105 units).

Another small RCT (published in Chinese – abstract only received) evaluated the effect of rFVIIa (40 µg/kg) versus placebo on the early recovery of 22 patients undergoing cardiac valve replacement under cardiopulmonary bypass.⁴⁰ The rFVIIa group received the drug after protamine reversal of heparin. Patients who received rFVIIa improved their coagulation function and received less blood transfusion compared with placebo.

Other studies and cases

There are numerous studies and cases of rFVIIa for uncontrolled bleeding following cardiac surgery (see Tanos and Dunning review for a summary).³⁷ Some of the most recent papers are summarised.

In Australia, there is a retrospective review of experience using rFVIIa (usual dose 90 µg/kg) for this condition in 53 patients.⁴¹ The patients had received conventional therapy and administration of rFVIIa produced reductions in the need for all blood products. There is also a retrospective analysis of 12 patients who received rescue therapy with rFVIIa (100 µg/kg), which showed that it achieved haemostasis within 30 minutes and reduced blood product usage considerably.⁴² An Australian retrospective chart review found that 10 patients responded to rFVIIa (median dose 85 µg/kg); however, mortality was high when rFVIIa was used after more than 24 hours, and continued bleeding in 6 episodes necessitated return to theatre where a surgical source of bleeding was found.⁴³

A case control study has reported the outcomes of 51 cardiac surgery patients who received rFVIIa for intractable blood loss and compared the results with 51 matched control patients.⁴⁴ Blood loss and blood product usage were substantially decreased after rFVIIa (2.4-4.8 mg) use during surgery and after sternal closure. Increased morbidity (renal dysfunction and length of ICU hospital stay) was observed with rFVIIa compared to controls. The authors suggest that rFVIIa may be an effective rescue therapy in these patients but that cautious use is advocated until RCT results become available.

Successful cessation of bleeding was achieved in 7 cardiac surgery patients with intractable bleeding, and 4 of these received lower doses than usual rFVIIa doses (26-40 µg/kg).⁴⁵ In a similar group of 15 patients, small-dose rFVIIa (1.2mg as a slow IV bolus at the end of complete step-by step transfusion protocol) was shown to reduce blood loss compared with an earlier non-rFVIIa group of matching patients.⁴⁶ A retrospective analysis in 24 patients found that rFVIIa (60 µg/kg) reduced blood loss and transfusion requirements; however, the results were not different between the rFVIIa group and a matching historic control group.⁴⁷

Other surgery

Overall recommendations

Level of evidence

There are 2 RCTs of the prophylactic use of rFVIIa in elective surgery with conflicting results. There are no RCTs of its use when uncontrolled bleeding occurs in surgical patients. Vincent et al reviewed case reports, which documented success with rFVIIa (80-120 µg/kg) and this document has summarised more recent papers (see below). In the systematic review section on pages 12-14, the following recommendations were made:

- rFVIIa was deemed appropriate in spinal surgery, hysterectomy when significant clotting factor replacement had failed).⁸
- rFVIIa may be used in uncontrolled bleeding in surgical patients (low level of evidence). It was not recommended for use in management of massive haemorrhage associated with elective surgery.¹²

Recommendations

Grade C: Therapeutic use of rFVIIa may be of benefit for patients with unexpected life-threatening bleeding as additional therapy to surgical and/or medical control of bleeding.

Grade D: Prophylactic use of rFVIIa in elective surgery cannot be recommended.

Reviews

No reviews specific to surgical patients were found.

RCTs

There are no RCTs for use of rFVIIa when uncontrolled bleeding occurs in surgical patients; however, there are 2 RCTs of its prophylactic use. In one study, there were 48 patients with normal haemostasis undergoing major pelvic-acetabular surgery who were given rFVIIa (90 µg/kg as an IV bolus) or placebo when the first skin incision was made.⁴⁸ The total volume of perioperative blood loss (primary outcome variable) was not significantly different between the groups and there were no differences in transfusion requirements (secondary outcome). The authors concluded that rFVIIa does not decrease the volume of perioperative blood loss in patients undergoing this procedure.

In the second study, blood loss and transfusion requirements in 36 patients undergoing retropubic prostatectomy, were assessed following rFVIIa (20 µg/kg or 40 µg/kg IV bolus) or placebo during the operation.⁴⁹ Median perioperative blood loss was significantly less in the treatment groups compared with placebo group (p=0.001). Seven of 12 placebo-treated patients required transfusion but only 3 who received 20 µg/kg rFVIIa and none who received 40 µg/kg required this. The authors concluded that rFVIIa can reduce perioperative blood loss and eliminate the need for transfusion in patients undergoing major surgery.

Vincent et al suggested that the reason for the opposing results in these 2 studies may be due to patient age and type/location of the surgery.¹² Also, the rFVIIa was administered later in the second study than in the first one, which may have affected drug activity.

Other studies and cases

Vincent et al reviewed case studies showing that rFVIIa was effective at stopping bleeding in surgical patients.¹² The following summaries are of more recent studies and cases and the results are similar.

In a retrospective review of 18 surgical or trauma patients who received rFVIIa (mean dose 100 µg/kg) for coagulopathic bleeding, all but 1 patient had resolution of bleeding and transfusion requirements for RBCs and plasma were substantially reduced after rFVIIa.⁵⁰ Another retrospective report looked at the use of rFVIIa in 40 consecutive patients, 21 of whom were surgical bleeding patients.⁵¹ Results were presented for 31 patients and 21 (68%) of those showed a reduction or cessation in bleeding (median surgical dose 78 µg/kg). Of 973 patients in one institution who underwent complex vascular surgery, there were 18 patients with intractable bleeding who were given rFVIIa (40-80 µg/kg) following failure with conventional measures.⁵² Twelve of 18 patients responded and survived the operation (improved haemodynamic stability and decreased transfusion requirements) while 6 died. The authors said rFVIIa should be administered early with measures to achieve haemodynamic stability and correction of acidosis.

Trauma

Overall recommendations

Level of evidence

Two multi-centre RCTs were conducted simultaneously to evaluate the efficacy and safety of rFVIIa in patients with severe blunt and/or penetrating trauma. In previous reviews cited below, there is consensus to use rFVIIa in trauma patients if bleeding continues after conventional therapy. However, the recommended doses are lower than was used in the RCT by Boffard et al. This RCT showed that rFVIIa significantly reduces RBC transfusion requirements in severe blunt trauma, and this trend also occurs in penetrating trauma.¹¹ Case series report that rFVIIa may be beneficial for uncontrolled bleeding in trauma.

In the systematic review section on pages 12-14, the following recommendations were made – all based on the RCT by Boffard et al:

- rFVIIa was deemed appropriate for severe multiple trauma if surgery and substantial blood replacement are unsuccessful.⁸
- rFVIIa reduced the number of trauma patients needing massive blood transfusion.⁹
- rFVIIa is recommended for control of bleeding in blunt trauma but is not recommended for use in management of massive haemorrhage associated with penetrating trauma.¹²

Recommendations

Grade C: rFVIIa maybe of benefit for patients with life-threatening bleeding in context of blunt trauma. Uncertainty exists regarding recommended dosage.

Grade D: Results for benefit of rFVIIa in penetrating trauma are conflicting. Surgical control of massive haemorrhage is the first line of management as rFVIIa appears less effective when very high RBC transfusion rates are required. rFVIIa may be of benefit for patients with life-threatening bleeding as additional therapy to surgical and/or medical control of bleeding.

Reviews

A recent review identified 126 rFVIIa-treated trauma patients reported in 15 publications up to November 2004.⁵³ Age range was from 20 months to 88 years and almost 70% had blunt injury. In most patients, rFVIIa was used after conventional methods had failed. Doses of rFVIIa varied from 36 to-178 µg/kg) and single and multiple doses (range 2-12h) were used. The effectiveness of rFVIIa (determined by reduction in blood loss, transfusion requirements and mortality) was reported in 80% of cases, and shortening or normalisation of coagulation parameters was also shown in most cases. Thus, the data

seems to support rFVIIa as an additional therapy for the reduction of haemorrhage and transfusion requirements in trauma patients.

In an Australian-based review of clinical experience with rFVIIa, the authors state their results have led to guidelines where rFVIIa (90 µg/kg) is recommended in trauma patients if uncontrolled bleeding continues after conventional therapy.⁵⁴ Similar guidelines have also been developed by the Israeli Multidisciplinary rFVIIa Task Force, based on literature review and the outcomes of the first 36 patients from a prospective registry who received rFVIIa for uncontrolled bleeding as a result of trauma (blunt, penetrating and blast incidents) in Israel.¹⁴ An initial dose of 120 µg/kg was advised by the authors. An Australian report of battlefield experience with rFVIIa and other haemostatic agents states that rFVIIa can stop some cases of severe bleeding due to coagulopathy in military situations.⁵⁵

RCTs

Two multi-centre RCTs were conducted simultaneously to evaluate the efficacy and safety of rFVIIa in patients with severe blunt and/or penetrating trauma.¹¹ Selected patients who had received 6 units of RBCs within 4 hours of hospital admission were randomised to receive 3 injections of rFVIIa (200 µg/kg followed by 100 µg/kg and 100 µg/kg, 1h and 3h after the first dose) or 3 similarly-timed placebo injections, immediately after the eighth transfusion of RBCs. The primary efficacy endpoint was the number of RBCs transfused in the 48h period following the first drug dose. In blunt trauma, RBC transfusion was significantly reduced with rFVIIa relative to placebo (estimated reduction of 2.6 RBC units, $p = 0.02$), and the need for massive transfusion (>20 units of RBCs) was reduced (14% vs 33% of patients; $p = 0.03$). In penetrating trauma, similar analyses showed trends toward rFVIIa reducing RBC transfusion (estimated reduction of 1.0 RBC units, $p = 0.10$) and massive transfusion (7% vs 19%; $p = 0.08$). Trends toward a reduction in mortality and critical complications were observed. Thus, rFVIIa resulted in a significant reduction in RBC transfusion in severe blunt trauma. Similar trends were observed in penetrating trauma. The authors commented that rFVIIa has the potential as an add-on to existing trauma therapy to directly break the deleterious cycle of coagulopathy, acidosis and hypothermia.

Other studies and cases

A retrospective cohort study was conducted among 242 trauma patients requiring transfusion of 8 or more units of packed RBCs within the first 12 hours of admission.⁵⁶ There were 38 patients who received rFVIIa and it was associated with improved 24-hour survival (adjusting for baseline demographics and injury factors). Also, there was a strong trend toward increased overall in-hospital survival. Subgroup analysis showed that 24-hour survivors required a slower initial rate of RBC transfusion, had higher platelet counts and smaller base deficits compared with rFVIIa patients who died during the first 24 hours. The authors said that rFVIIa may be able to improve the early survival of massively bleeding trauma patients but they stated that surgical control of massive haemorrhage is still first-line, as rFVIIa seemed to be less effective when very high RBC

transfusion rates were required. Correction of acidosis and thrombocytopenia may also be key factors in determining rFVIIa efficacy.

In one study, 81 coagulopathic trauma patients treated using rFVIIa were compared with a control group from a trauma registry.⁵⁷ The cause of coagulopathy included acute traumatic hemorrhage (46 patients), traumatic brain injury (20), warfarin use (9), congenital Factor VII deficiency (2), and other acquired haematological defects (4). Dosage of rFVIIa was 40 to 150 µg/kg. Coagulopathy was reversed in 75% of cases. In a similar study of 29 patients with traumatic haemorrhage (25 with blunt trauma), rFVIIa (40 µg/kg, repeated once if necessary) resulted in significantly less RBC, platelet, and cryoprecipitate use when compared with the matched controls.⁵⁸ Similar success has been reported with rFVIIa in smaller studies of uncontrolled bleeding after trauma.⁵⁹⁻⁶¹

Intracerebral haemorrhage

Overall recommendations

Level of evidence

There is one RCT in ICH in adults, which looks at efficacy of rFVIIa in 399 patients. It is described as a dose-ranging proof-of-concept trial, and the authors state that a further trial is underway to better define dosage and identify patients at risk of thromboembolic complications. There are no comparable studies from other centres. In the systematic review section on pages 12-14, the following statements are made:

- rFVIIa is appropriate for non-traumatic intracranial bleeding (only if less than 4 hours has elapsed since symptom onset or if traumatic bleeding is associated with anticoagulant use and haematoma expansion).⁸ This recommendation is based solely on the ICH study in 399 patients.
- rFVIIa showed a significant reduction in mortality among patients with ICH.⁹ The authors are referring to the ICH study in 399 patients.

Recommendation

Grade B: It is reasonable to consider use rFVIIa in the management of ICH if it can be given within 4 hours of symptom onset. It should be noted, however, that this recommendation is based on a single RCT in comparison with placebo and efficacy in comparison with other therapies has not been tested. At this point in time, use should only be considered where standard therapy is not a reasonable option and as part of a clinical trial. Concern exists regarding thromboembolic complications at dosages beyond 80 µg/kg. Use with caution in patients with risk factors for thromboembolic disease.

Reviews

There are 2 recent reviews written by the research group that conducted the RCTs in this area. The authors state that the key to successful ICH treatment is to limit the haematoma growth within the first few hours of onset and thus minimise or prevent neurological deterioration, which is a predictor of increased mortality. They suggest that ultra-early therapy with rFVIIa could be useful for this and cite their own RCT in 399 patients (see below) where the best outcomes were achieved within 3 hours of symptom onset.^{62, 63}

They say a phase 3 trial is currently underway in 675 ICH patients to determine if emergency intervention with early use rFVIIa (20 or 80 µg/kg) is feasible.

RCTs

There are 3 RCTs, 2 of which are phase 2 studies that investigated escalating doses of rFVIIa and reported safety data.^{64, 65} In the remaining study, 399 patients with ICH (diagnosed by CT within 3 hours after onset) were given rFVIIa (40, 80 or 160 µg/kg) or placebo within 1 hour of diagnosis in an attempt to limit haematoma expansion.¹⁰ Haematoma volume increased more in the placebo group (29% at 24 hours) than in the

rFVIIa groups (11%-16%, $p=0.01$). Death or disability (secondary endpoint assessed at 90 days) was also significantly reduced in the rFVIIa groups (49%-55%) compared to placebo (69%, $p=0.004$) as was 90-day mortality (29% vs 18%, respectively, $p=0.02$). The authors concluded that treatment with rFVIIa within 4 hours after the onset of ICH limits the growth of the haematoma, reduces mortality, and improves functional outcomes at 90 days. There was a small dose-related increase in the frequency of thromboembolic adverse events, which may have occurred due to prolonged rFVIIa levels because of the relatively low bleeding rate compared with trauma.¹²

Other studies and cases

There is one study of rFVIIa in warfarinised patients with acute ICH, which is summarised in the next section.

Reversal of vitamin K antagonist (warfarin) therapy

Overall recommendations

Level of evidence

There are no RCTs that investigate the use of rFVIIa in managing haemorrhage in warfarinised patients. The remaining literature consists of non-controlled studies and cases that show rFVIIa can normalise the INR in warfarinised patients; however, this information needs to be verified in controlled studies.

In the systematic review section on pages 12-14, only the Shander paper covers reversal of anticoagulant therapy. It cites most of the studies covered in this review, but does not make a specific recommendation apart from stating that rFVIIa is appropriate for use in non-traumatic intracranial bleeding if it is given within 4 hours of symptom onset in patients who may or may not have been given warfarin. The role of rFVIIa in head trauma is uncertain.

Effective reversal of warfarin effect is readily achieved by the combination of cessation of warfarin, vitamin K, plasma or factor concentrate infusion depending on the clinical circumstances. Effective rapid reversal of warfarin effect in cases of serious haemorrhage can be achieved by prothrombin complex concentrates and plasma infusion. The prothrombin complex concentrate available in Australia has a low content of Factor VII so fresh plasma must also be transfused. These therapies are indicated for this purpose. These therapies also replace other vitamin K dependent coagulation factor deficiencies, especially Factor II, which are important contributors to bleeding in warfarinised patients. Given these considerations, rFVIIa has no primary role in the reversal of anticoagulation in patients taking warfarin. There maybe a role of an off-label use of rFVIIa in the context of ICH or life-threatening haemorrhage not controlled by surgical or medical therapies.

Recommendation

Grade C: while rFVIIa would be expected to partially reverse the effect of warfarin, effective therapies which correct all warfarin-induced factor deficiencies are available. Off-label use of rFVIIa should only be considered in context of ICH (see above)

Reviews

The systematic review by Levi et al summarised studies up to July 2004 on this topic (see below for summary).⁷ They commented that the duration of effect of rFVIIa is short (2-3 hrs) and that alternative treatment with prothrombin complex concentrates will correct not only a deficiency of Factor VII but also deficiencies of other vitamin K proteins. In a more general review, the same research group said that rFVIIa may become a therapeutic option to reverse anticoagulation in cases of severe bleeding or in patients scheduled for emergency surgery but that more investigation is required.

Shander et al stated that rFVIIa was appropriate to use in non-traumatic intracranial bleeding within 4 hours of symptom onset, with or without taking warfarin, and for isolated traumatic head injury if there was evidence of expanding bleeding in patients taking warfarin.⁸

RCTs

There are no RCTs of rFVIIa in patients taking warfarin.

Other studies and cases

Levi et al summarised the non-controlled studies and case reports about reversal of anticoagulant therapy with rFVIIa as follows.⁷ In healthy volunteers treated with acenocoumarol, the prolonged international normalised ratio (INR) was normalized by rFVIIa at doses between 5 and 320 µg/kg.⁶⁶ Doses of rFVIIa greater than 120 µg/kg resulted in normalisation of the INR that lasted over 24 hours. Six patients on warfarin prophylaxis developed overt CNS bleeding and were given rFVIIa (10-40 µg/kg).⁶⁷ It reversed anticoagulation, arrested bleeding, and allowed surgical drainage of the haematoma in all patients. A study in 13 warfarinised patients undergoing invasive procedures showed that rFVIIa (15-90 µg/kg) normalised the PT and corrected the prolonged INRs in all subjects.⁶⁸

There are also recent studies confirming that rFVIIa is effective in warfarin-induced anticoagulation. The effects of rFVIIa were studied in a consecutive series of 7 elderly patients with symptomatic, non-traumatic warfarin-related acute ICH.⁶⁹ The INR decreased rapidly from a mean of 2.7 to 1.08 after administration of rFVIIa (mean dose 62.1 µg/kg). Five of the 7 patients survived and were discharged from hospital with severe disability (Glasgow Outcome Scale, 3). Reversal was successfully achieved in a single patient with elevated INR and PT prior to rt-PA in acute stroke.⁷⁰ Another case involved an elderly male patient with an aortic prosthetic valve, chronic lymphocytic leukaemia and recently developed metastatic lung cancer.⁷¹ The patient developed a major gastrointestinal bleed as a result of an elevated INR (>8) due to warfarin. He received rFVIIa (50 µg/kg) which corrected the INR to 2.1 and bleeding ceased. A retrospective chart review of 28 patients with warfarin-associated ICH treated in a neurology/neurosurgery intensive care unit was recently published.⁷² There were 12 evaluable patients who were given rFVIIa (dose range 2.4-9.6mg) after vitamin K and FFP because they were classified as high risk. The results showed rFVIIa shortened the time to correction of INR and reduced the total dose of FFP. In a retrospective controlled study, rFVIIa was used as a second-line therapy for reversal of coagulation (mainly warfarin) in 29 neurosurgical patients after initial attempts at reversal with FFP had failed.⁷³ After rFVIIa (1.4 mg), the mean INR decreased and normalized within 7 hours. The number of patients with good functional outcome (Glasgow Outcome Scale score of 5) was greater among patients treated with rFVIIa compared with those in a matched group who received only vitamin K and FFP. There were 6 deaths in each group.

Reversal of anticoagulant therapy due to heparin, antiplatelet and novel antithrombotic agents

Overall recommendations

Level of evidence

There are 3 small RCTs that investigated the use of rFVIIa in reversing the anticoagulant effect of idraparinux, fondaparinux and melagatran respectively. These studies were in healthy volunteers without bleeding complications. While the positive results in the first 2 studies were stated as promising by the authors, the third study did not show any benefit. The remaining literature consists of non-controlled studies and cases.

Systematic reviews make little mention of this topic. Shander et al state that rFVIIa is appropriate for use in non-traumatic intracranial bleeding if it is given within 4 hours of symptom onset in patients who may or may not have been given low molecular weight heparin (LMWH), and in isolated traumatic head injury where there is evidence of expanding bleeding and patients prescribed LMWH.

Recommendation

Grade D: While of potential benefit, there is insufficient evidence for a primary role of rFVIIa in reversal of anticoagulation with heparin-like molecules and novel anticoagulant agents.

Reviews

Shander et al stated that rFVIIa was appropriate to use in non-traumatic intracranial bleeding within 4 hours of symptom onset, with or without taking warfarin or a LMWH, and for isolated traumatic head injury if there was evidence of expanding bleeding in patients taking warfarin or LMWH.⁸ While they also described the pentasaccharide studies^{74, 75} and other studies also described below,^{66-69, 76} they did not specifically recommend a primary use in reversing anticoagulant therapy.

RCTs

An RCT (placebo-controlled crossover trial) was conducted in 12 healthy volunteers to investigate the use of rFVIIa as an antidote to the long-acting anticoagulant agent, idraparinux.⁷⁵ One injection of rFVIIa (90 µg/kg, 3h or one week after 7.5mg idraparinux) normalised the prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT) and reversed the decrease in markers for thrombin generation. Therefore, rFVIIa may reverse the peak and trough anticoagulant effects of idraparinux. This result is consistent with a similar study using fondaparinux.⁷⁴ Thus, rFVIIa may be an antidote to the pentasaccharide anticoagulants if serious bleeding complications arise though studies in actual patients are required.

In a more recent RCT (single-blind, parallel-group) in 47 healthy males, rFVIIa (90 µg/kg) or placebo was given 1 hour after the start of melagatran (12.5mg) infusion.⁷⁷ It did not reverse the melagatran-induced effects on activated partial thromboplastin, thrombin generation, and platelet activation. The authors suggest further investigation to see if repeated, continuous or higher doses of rFVIIa might be effective.

Other studies and cases

A more recent case report shows how combined single doses of rFVIIa (90 µg/kg) and tranexamic acid (15 mg/kg) were effective in controlling severe postoperative bleeding after fondaparinux.⁷⁸ The 79-year old patient had been given fondaparinux to prevent deep vein thrombosis after hip surgery but he developed haemorrhagic shock and bleeding could not be stopped by conventional measures. There is a recent report of 2 cases of severe sepsis treated with drotrecogin-alpha where massive perioperative haemorrhage (unresponsive to conventional treatment) was treated with rFVIIa (40 µg/kg).⁷⁹ The authors state that effective haemostasis was achieved with 2 doses of rFVIIa.

Paediatrics

Overall recommendations

Level of evidence

There are many clinical scenarios where rFVIIa has been used in paediatrics; however, the studies are in small numbers of patients or in individual cases. Thus, the evidence base for using rFVIIa in children is very limited. This section contains details from many low levels of evidence and the information should be regarded with that in mind.

Recommendation

Grade D: The evidence base for using rFVIIa in children is very limited. There are recognised difficulties in conducting appropriate studies to obtain good evidence in paediatrics as well as uncertainties regarding dosing. The only published RCT in the paediatric population (cardiac surgery for congenital heart disease) showed no benefit of rFVIIa prophylaxis and possibly harm, with significantly prolonged time to chest closure in the rFVIIa treated group. rFVIIa may be of benefit for paediatric patients with life-threatening bleeding in the context of trauma, surgery, liver disease and prematurity when used as additional therapy to surgical and/or medical control of bleeding. However, its use is not recommended in patient populations where there is a risk of thromboembolism (eg trauma, congenital heart disease, other hyperviscous or hypercoagulable states, presence of arterial or central venous catheters).

Reviews

Mathew and Young have recently reviewed the role of rFVIIa in both haemophilia and non-haemophilia bleeding conditions in children.⁸⁰ They state there is a paucity of high levels of evidence for its off-label use in paediatrics, and that extrapolation of results in haemophiliac children is not possible because of publication bias. They have attempted to consolidate results from available studies because they say it is unlikely that clinical trials in children will be conducted or completed. The studies suggest that rFVIIa may reduce or arrest bleeding and thus may be useful in eliminating coagulopathy in surgical haemorrhage, brain injury or sepsis so that resuscitation and surgical correction of anatomical defects may be completed. However, there remain many unknown efficacy and safety issues with the drug. The following summary of studies has been compiled from the review by Mathew and Young together with recent studies identified by the literature search strategy.

Studies and cases

Liver disease

The evidence in liver failure or transplantation is all from cases or case series. In one case, an 11-month old with total parenteral nutrition-induced cholelithiasis and chronic

coagulopathy developed upper GI bleeding, which did not stop after FFP administration.⁸¹ Administration of rFVIIa (90 µg/kg) corrected coagulation and the bleeding subsided. Prophylactic rFVIIa has also been successful in children with liver failure who underwent endoscopic procedures of liver biopsy.^{82,83} In a study of 12 children with liver disease, rFVIIa (median dose 66 µg/kg) decreased bleeding in 10 of 22 children with life-threatening bleeding (where conventional therapy had failed) and may have prevented bleeding complications in all 7 children who underwent invasive procedures.⁸⁴ Similar success was reported in a study of children with liver failure where rFVIIa produced rapid cessation of bleeding after conventional therapy had failed.⁸⁵

A retrospective review of 89 children who underwent liver transplant showed that prophylactic rFVIIa given to a cohort of 28 children with high risk of operative bleeding reduced their risk to a similar level of a cohort of 61 children with no identified risk of bleeding.⁸⁶ In a case series, the use of rFVIIa in 7 children presenting with coagulopathy and nonsurgical bleeding after liver graft reperfusion is described.⁸⁷ A single dose of rFVIIa (mean 68 µg/kg, aprotinin or tranexamic acid given simultaneously) reversed severe coagulopathy developing after graft reperfusion and produced effective haemostasis in liver transplant recipients.

There is a recent report of rFVIIa use in 2 children, one with end-stage renal disease (14 years old) and one with liver failure (9 months old), who had compartment syndrome related to life-threatening bleeding complications.⁸⁸ In the first case, rFVIIa (90 µg/kg) successfully stopped bleeding and pain, paraesthesia and sensory/motor dysfunction resolved within hours. The fasciotomy site was closed 5 days later without complication. In the second case, 2 bolus infusions of rFVIIa (90 µg/kg at 4h interval) produced cessation of bleeding after the second infusion and the compartment syndrome resolved within 4 hours. Scheduled fasciotomy was cancelled. However, the patient died one month later of fulminant liver failure.

Cardiac surgery

There is an RCT from Australian investigators on the effectiveness of prophylactic administration of rFVIIa (40 µg/kg, a second dose was administered if bleeding was excessive and also given post surgery if postoperative bleeding occurred) for cardiopulmonary bypass surgery in children under 1 year old with congenital heart disease.⁸⁹ The primary endpoint was time to chest closure following reversal of heparin with protamine sulphate and secondary endpoints were volume of transfused blood, platelet concentrates and FFP. No benefit of rFVIIa prophylaxis was found in the time to chest closure, which was significantly prolonged in the rFVIIa group compared with the placebo group. Also, there were no significant differences in the secondary endpoints. The authors could not explain why prolonged chest closure occurred with rFVIIa.

All of the other evidence in cardiac surgery is from case reports. Cessation of postoperative bleeding has been documented in several cases and case series.⁹⁰⁻⁹² Also, there are case series showing rFVIIa is successful (after failure of conventional treatment)

at stopping bleeding following cardiac surgery with cardiopulmonary bypass (30-60 µg/kg, up to 4 doses),⁹³ after open-heart surgery (90 µg/kg)⁹⁴ and at reducing chest tube output after cardiac surgery.⁹⁵ Mathew and Young comment that the potential for thrombotic episodes in this population group (though not evident in these cases) dictates rFVIIa be used only when no other option is available, or should be limited to clinical trials.⁸⁰

Preterm/term infants

There are several case reports where rFVIIa has been used in a desperate attempt to cease bleeding after standard therapies had failed.⁸⁰ A case report documents successful use of rFVIIa (50 µg/kg every 3h) for severe pulmonary haemorrhage in a very low birth weight infant.⁹⁶

A prospective, single-arm pilot study of 10 preterm infants between 23 and 28 weeks of gestation investigated the prophylactic use of rFVIIa in intraventricular haemorrhage (IVH).⁹⁷ This study was not powered to determine efficacy or adverse effects; however, the authors stated that administration of rFVIIa (100 µg/kg 4h for 72h) did not cause any adverse events and 20% of the neonates went on to have grade III or IV IVH, which is similar to the rate in studies in which rFVIIa was not given. A recent review highlighted the potential risk of thrombosis with use of rFVIIa for prevention of IVH in preterm infants and suggested that a prospective RCT was required before any recommendation on its use in this area could be made.⁹⁸

A case series of 9 infants, aged between 2 days to 4 months, with coagulopathy and bleeding treated with rFVIIa has been recently published.⁹⁹ The infants all suffered acute life-threatening haemorrhage: 2 were postoperative from cardiac surgery, 2 had Vitamin K deficiency and intracranial haemorrhage, 3 had suspected necrotizing enterocolitis and abdominal haemorrhage, and 2 had pulmonary haemorrhage. Seven of the 9 patients had FFP, cryoprecipitate, or platelet administration in failed attempts to correct the coagulopathy prior to being given rFVIIa (dose range 90-100 µg/kg). Clinical resolution of bleeding occurred in all patients after receiving rFVIIa, and 7 of 9 patients survived.

A recent report shows how 3 cases of acute life-threatening peri- and postnatal haemorrhage were successfully controlled after the application of rFVIIa.¹⁰⁰ All infants were first treated with vitamin K, fresh-frozen plasma and platelet transfusion. The cases substantiate other reports that rFVIIa is an effective treatment for acute, refractory and life-threatening bleeding in neonates and premature infants.

Trauma

Trauma data in children are scant. Mathew and Young point out that patients who are haemorrhaging are also at high risk of thrombosis and must be monitored for this if they are given rFVIIa.⁸⁰ Also, any further doses of rFVIIa once haemostasis is achieved in this patient group maybe harmful compared with most other indications listed in this section. Of the 36 trauma patients in the Martinowitz paper (see trauma section above), there were

13 who were 14 to 18 years old. They had suffered massive life-threatening bleeds that failed to stop despite conventional treatment; however, 12 responded to rFVIIa and 3 died (one from blood loss and 2 from sepsis).¹⁴ In the series of 81 coagulopathic patients reported by Dutton et al (see trauma section above), 17 were 18 years old or younger.⁵⁷ Reversal of coagulopathy by rFVIIa was achieved in 75% of patients and 6 of the 17 paediatric patients died. Three paediatric patients suffered severe coagulopathy after cerebral injury.¹⁰¹ Administration of rFVIIa (90 µg/kg as initial therapy or after failed conventional therapy) produced rapid and successful correction of coagulopathy. In 2 children with traumatic liver injuries, rFVIIa (50 µg/kg every 2h, following failed conventional therapy) was successful in achieving haemostasis.¹⁰²

Surgery

Four cases of rFVIIa use (100-200 µg/kg every 2h) in paediatric patients (term infant, 3, 9 and 18 years) with 'surgical-type' bleeding has been reported.¹⁰³ Bleeding was stopped in 2 of the patients with liver and GI bleeding but not in the other patients (GI bleed and graft vs host disease).

In a retrospective review, there were 4 patients (3 neonates and a 3-year old boy) who received rFVIIa for refractory bleeding on extracorporeal membrane oxygenation (ECMO) following open heart surgery.¹⁰⁴ Administration of rFVIIa (90-120 µg/kg) decreased bleeding within 30 minutes and was repeated as a prophylactic measure after 4 hours. Overall transfusion requirements fell substantially in all patients. Successful use of repeated doses of rFVIIa was reported in a further 2 patients on ECMO (11-year old after heart transplant and a 13-year old with cardiopulmonary failure).¹⁰⁵ There is also a case of a 4-year-old girl who suffered severe postoperative chest tube drainage bleeding after cardiac transplant surgery requiring extracorporeal membrane oxygenation.¹⁰⁶ After failed standard therapy, rFVIIa (180 µg/kg) controlled the haemorrhage.

The efficacy of rFVIIa was evaluated retrospectively in a series of 26 patients (mean age 16.6 years) with scoliosis undergoing correctional surgery. The results were compared with matched controls who received standard therapy. Intra-operative and combined intra-operative and postoperative blood losses were significantly smaller in the rFVIIa-treated group (mean dose 23 µg/kg, 30min before start of surgery) than in the historical controls. There was also reduced blood loss per vertebral segment fused and per hour of surgery. The authors suggested that rFVIIa is an effective haemostatic agent for spinal fusion surgery in adolescent patients with idiopathic scoliosis.¹⁰⁷

Other uses

Mathew and Young present many other individual cases of rFVIIa use in children. There is an RCT of the efficacy and safety of rFVIIa (100 µg/kg, repeated at 30 minutes if necessary) in 25 patients less than 18 years old with grade II or III Dengue haemorrhagic fever (DHF) who required blood component therapy for controlling bleeding episodes.¹⁰⁸ Patients received conventional therapy as well as rFVIIa. Two hours after administration, there was complete cessation of bleeding in 75% of rFVIIa patients versus 44% on

placebo. Cumulative use of RBCs was not different between the groups but the need for platelet concentrate was lower among rFVIIa patients. This study confirmed an earlier study by the same authors that rFVIIa might be a useful additional treatment to blood component transfusion for controlling active bleeding in children with DHF especially when platelet concentrate was not readily available.¹⁰⁹

Safety

Overall recommendations

Level of evidence

One RCT found a rFVIIa dose-related increase in thromboembolic events.¹⁰ Other prospective studies, many underpowered to detect differences in thromboembolic adverse events, have not found differences between patients receiving or not receiving rFVIIa.

- There was a non-significant trend towards increased mortality and thromboembolic serious adverse events in some trials in the adult population (eg, liver transplant, upper GI bleeding, stem cell transplantation).⁹
- The only published RCT in the paediatric population (cardiac surgery for congenital heart disease) showed no benefit of rFVIIa prophylaxis and possibly harm, with significantly prolonged time to chest closure in the rFVIIa treated group

Recommendation

There are conflicting results regarding the thromboembolic risk of rFVIIa. Uncertainty exists regarding the magnitude of this risk and possible pre-disposing factors for thromboembolism to guide clinicians in patient selection. Patients and their families should be aware of this potential complication, especially in cases of off-label usage. Well-designed prospective studies are required to address this important issue.

Review of literature

Thromboembolic adverse events are of greatest concern with rFVIIa use. This is especially in patients with a previous history of thrombosis or with risk factors for thromboembolic disease. The simultaneous use of activated prothrombin complex concentrates or the presence of sepsis may also contribute to the occurrence of thrombosis; however, Levi et al report use of rFVIIa in several cases where DIC was present without untoward outcome.⁷ Nevertheless, patients with an underlying pathology that predisposes thrombosis should be carefully monitored before, during and after rFVIIa therapy.¹¹⁰

Most of the prospective studies have not shown an increase in thromboembolic events with rFVIIa compared with placebo. These RCTs have however been underpowered to detect a difference in most cases.^{11, 24, 29-32, 48, 49} In the study of rFVIIa in ICH by Mayer et al, a significant increase in thromboembolic events was reported most notably at the highest rFVIIa dose (10% at 160 µg/kg, 2% for placebo).¹⁰ Vincent et al proposed that rFVIIa clearance is relatively low in ICH because of the low bleeding rate compared with the severe bleeding seen in conditions such as trauma. Thus, adverse events may be seen with high dose rFVIIa in patients without severe bleeding.¹²

In the CADTH systematic review, mortality rates associated with rFVIIa and placebo groups in the various RCTs are given.⁹ In some of the studies mortality rates are higher in the rFVIIa groups though statistical significance was not found in any of the studies. The Cochrane group found a trend for reduced mortality with therapeutic use of rFVIIa in a pooled analysis of 7 RCTs, RR 0.82 (95% CI 0.64-1.04).¹¹¹ Similar analyses by the same authors, however, showed a trend against rFVIIa with respect to thromboembolic adverse events: RR 1.25 (95% CI 0.76-2.07) for prophylactic use, RR 1.50 (95% CI 0.86-2.62) for therapeutic use.

In an observational study of 655 cardiac surgery patients with excessive bleeding, adverse event rates were compared in 114 patients who met the criteria for rFVIIa therapy (mean dose 56 µg/kg) with 541 who did not require rFVIIa.¹¹² After adjustment for confounders, rFVIIa was not found to be associated with an increased risk of adverse events, and early rFVIIa treatment (ie, ≤8 units RBC before treatment) was associated with better outcomes than later treatment. In a previous and smaller study by the same investigators, an increased frequency of acute renal failure was observed in cardiac surgery patients who received rFVIIa, but the authors admitted no definitive conclusions could be drawn because of the small sample size.⁴⁴

In the systematic review by Levi et al, they estimate the incidence of thromboembolic events from all cases at 1.4% in non-haemophilia patients, and state it is probably lower than this when all of the RCT data is added.⁷ A review of critical safety data obtained from 13 Novo Nordisk-sponsored clinical trials of rFVIIa in patients with coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury showed that thrombotic adverse events were reported for 5.3% (23/430) of placebo-treated patients and 6.0% (45/748) of patients on active treatment. No significant difference was found between placebo-treated and rFVIIa-treated patients with respect to the incidence of thrombotic events, either on an individual trial basis or for all the trials combined (p = 0.57).¹¹³

O'Connell et al looked at the US Food and Drug Administration Adverse Event Reporting System for approved and off-label use of rFVIIa between March 1999 and December 2004.¹¹⁴ There were 168 of 431 reports that described 185 thromboembolic events. Off-label use accounted for 151 of the reports, most with active bleeding (n=115). Reported adverse events were thromboembolic cerebrovascular accident (n=39), acute myocardial infarction (n=34), other arterial thromboses (n=26), pulmonary embolism (n=32), other venous thromboses (including deep vein thrombosis) (n=42), and clotted devices (n=10). In 36 (72%) of 50 reported deaths, the probable cause of death was the thromboembolic event. Further analysis showed that 73 events (52%) occurred in the first 24 hours after the last dose (30 events within 2 hours). Most of the reports lacked sufficient information to fully evaluate potential dosage associations, and the authors stated that RCTs are needed to establish the safety of rFVIIa in nonhaemophilic patients.

Post haemorrhagic hydrocephalus was recently reported in 5 of 9 ICH cases treated with rFVIIa.¹¹⁵

The Haemostasis Registry has published latest workshop results (April 2007, <http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html>), which show that thromboembolic adverse events were possibly (31 cases) or probably (4) linked to rFVIIa therapy among 1127 cases – ie, total of 3% of cases.

Adverse Drug Reactions Advisory Committee (ADRAC) reports

As of 4 May 2007, ADRAC had received 72 reports (44 cases) of reactions related to rFVIIa – there were 11 deaths (8 cases) and it was the sole-suspected medicine in 51 reactions (30 cases). Most frequently reported reactions (total, death, sole-suspected) are shown in table 2.

Table 2. ADRAC reports of reactions related to rFVIIa

Reaction	Total	Death	Sole suspected
All reported reactions	72	11	51
Thrombosis- includes arterial thrombosis, deep vein thrombosis, venous thrombosis	11	0	5
Cerebral artery thrombosis, cerebral infarct and cerebrovascular accident	10	2	6
Multi-organ failure	5	2	4
Pulmonary embolism	5	2	3
Myocardial infarction	5	0	3

Optimum dosages and timing of administration

Overall Recommendation

A recommendation for a fixed dosage of rFVIIa for off-label indications is not currently possible. Guidance about which patients should receive multiple doses of rFVIIa is also not currently possible.

Review of literature

Dosages of rFVIIa have been stated in each of the previous sections but no definite guidelines may be given because of the lack of well-designed studies. In the evidence-based review by Shander et al, the consensus panel recommended a dosage range of 41 to 90 µg/kg of rFVIIa for all off-label uses.⁸

Further studies that have specifically looked at dosage are as follows. A retrospective, multicentre chart audit of 315 nonhaemophiliac patients showed that rFVIIa was given for prevention of bleeding (primarily related to an impending surgical or invasive procedure, 38% of patients) or for treatment of bleeding (62%). There were 89% and 74% of patients with existing coagulopathy in the prevention and treatment groups, respectively. The median doses for prevention and treatment were 76 and 89 µg/kg, respectively. Bleeding was rare with prophylactic rFVIIa (14% bled within 6 hours of their procedure). In the treatment group, 53% stopped bleeding within 6 hours but 26% experienced re-bleeding and 37 patients died from bleeding within 48 hours after rFVIIa administration, which is less than reported in case series in the literature and may have been related to pH or publication bias.¹¹⁶ Khan et al performed a retrospective cohort study of 13 patients with life-threatening haemorrhage (in trauma and postoperative patients) who had no known history of coagulopathic disorders.¹¹⁷ Administration of rFVIIa occurred after conventional methods had failed. The authors used a standard dose of 90 µg/kg in 6 patients but noted that a reduced dose in a further 5 patients was also effective at stopping bleeding (overall average dose was 76 µg/kg).

Patient selection

Recommendations

A universally beneficial effect of rFVIIa in non-haemophilic conditions may not be expected, not only because of the wide variation in bleeding conditions but also because of patient characteristics. Administration of rFVIIa may stem bleeding in some patients but they still die of shock or re-bleeding.

A recommendation or guidance on which patients will likely benefit from rFVIIa treatment is not currently possible.

Review of literature

In a retrospective study, rFVIIa (50 or 100 µg/kg) use was reviewed among 46 patients with acute haemorrhagic shock as a result of blunt or penetrating trauma.¹¹⁸ Cessation of bleeding was the determinant of clinical response. There were 20 patients with a transient response who died, and 26 patients who did respond to rFVIIa therapy (8 of these died later). Independent predictors of successful response were the PT at time of administration and the revised trauma score (RTS) at the time of hospital admission. Younger age and injuries in one body area only were also associated with better outcomes. The authors stated that patients with profound haemorrhagic shock (low RTS, elevated PT or profound metabolic acidosis) were unlikely to respond to rFVIIa therapy. These results confirm earlier experiments, which showed that rFVIIa activity was reduced in acidosis (but not hypothermia),¹¹⁹ and the authors agreed that “last-ditch” administration of rFVIIa is unlikely to be beneficial.¹²⁰

Predicting response has also been measured by looking at mortality. In a study of 18 patients with severe haemorrhage, the 6 survivors had lower organ failure scores than the 12 who died, and they also tended to respond to one rFVIIa dose (90 µg/kg) with a significant reduction in blood product requirements.¹²¹ PT or APPT did not predict survival. The authors suggest that organ failure assessment may be useful when considering rFVIIa treatment. A clinical scoring system was devised in another study of 36 patients with uncontrolled surgical, traumatic or obstetric bleeding.¹²² The score was based on presence of coagulopathy, renal impairment, hypothermia, transfusion of RBCs and age. Death occurred in 19 patients. Survival was more likely in younger than older patients, those with less co morbidities and in patients who had needed least RBCs prior to rFVIIa administration, though the authors admitted that more work was required to better define which patients are the most suitable for therapy.

The Haemostasis Registry has published latest workshop results (April 2007, <http://www.med.monash.edu.au/epidemiology/traumaepi/haemostasis.html>), which show that pH, platelet level, context of bleeding and APTT provide the best predictive model of patient mortality. The following results have been presented:

- patients with pH lower than 7.2 were significantly more likely to die than those with normal pH (OR = 3.8, 95% CI = 1.9-7.6)
- patients with platelet levels less than 100 were significantly more likely to die than those with 'normal' platelet levels >149 (OR = 2.9, 95% CI = 1.3-6.5)
- obstetric patients were more likely to survive (OR = 0.08, 95% CI = 0.01-0.4) than trauma patients whereas haem/oncology patients were more likely to die than trauma patients (OR = 9.2, 95% CI = 2.6-33.7)
- patients with high APTT (38.1-80.0) were more likely to die than those with 'normal' APTT (≤ 38.0) (OR = 2.8, 95% CI = 1.3-5.8) as were patients with very high APTT (>80.0) (OR = 6.9, 95% CI = 2.7-17.6).

Cost considerations

rFVIIa is a high-cost drug. In Australia, the current price of NovoSeven (2006-7 financial year) is \$1238.46 per 1.2mg vial, \$2476.92 per 2.4mg vial and \$4953.84 per 4.8mg vial (all GST exclusive prices, personal communication Novo Nordisk). In some conditions, repeated doses may be required. Thus, its judicious use is obvious. Cost-effectiveness data for rFVIIa does not exist for most occasions of off-label usage.

The aim of one UK study was to assess the lifetime cost-effectiveness of rFVIIa versus placebo for control of bleeding in patients with severe blunt trauma. The authors developed a cost-effectiveness model based on patient level data from a 30-day international, RCT. The data were supplemented with secondary data from UK sources to estimate lifetime costs and benefits. A baseline estimate of the incremental cost per life year gained with rFVIIa, relative to placebo was £12613. The incremental cost per quality adjusted life year (QALY) gained was £18825 (both estimates are sensitive to the choice of discount rate and health state utility values used). Thus, rFVIIa may be a cost-effective therapy to the UK National Health Service.¹²³

In one US study, the cost-effectiveness of early treatment with rFVIIa for ICH was examined using a decision-analytic model.¹²⁴ Treatment of ICH with rFVIIa (40 µg/kg and 160 µg/kg) appeared to be cost effective (\leq \$50 000/QALY). At the 80 µg/kg dose, rFVIIa was not only cost effective, but also cost saving. Investigators in New Zealand reviewed blood transfusion over a 12-month period and assessed the major costs associated with haemorrhage management. A pharmacoeconomic evaluation of rFVIIa intervention for large volume transfusion was conducted to identify the most cost-effective strategy for using rFVIIa. Intervention with rFVIIa was most cost effective relatively early in the RBC transfusion period - the optimal time point is when 14 RBC units have been transfused.¹²⁵

In an economic analysis of the RCT, which showed that a single injection of rFVIIa could reduce perioperative blood loss and eliminate the need for transfusion in patients undergoing abdominal prostatectomy, it was concluded that rFVIIa (40 µg/kg) lowered overall treatment costs and reduced surgery time by conferring transfusion freedom.¹²⁶

General recommendations

Initial surgical and/or medical management of life-threatening bleeding should be undertaken according to a clearly defined protocol that includes:

- Identification and correction of any reversible defect (such as hypothermia and acidosis)
- Surgical intervention or embolism if required
- Appropriate transfusion of blood components (ie, packed red blood cells [RBCs], fresh frozen plasma [FFP], platelets, cryoprecipitate). In the case of paediatric patients, specialist paediatric haematology advice should be sought
- Reversal of the anticoagulant effects of heparin (protamine sulphate)
- Reversal of the anticoagulant effects of warfarin (prothrombinex-HT and vitamin K)
- Administration of pharmacological agents (eg, aprotinin and fibrinolytic inhibitors)
- Regular monitoring of FBC, PT, APTT, fibrinogen and D-dimer.

In patients with continued life-threatening bleeding despite appropriate conventional surgical and/or medical treatment to control bleeding, rFVIIa may be considered as additional therapy. The amelioration of coagulopathy thrombocytopenia (target platelets $>50,000 \times 10^9/L$), coagulopathy (target fibrinogen $>1.0 \text{ g/L}$), acidosis (pH >7.2) anaemia (haematocrit $>24\%$), and hypothermia are desirable for rFVIIa to be effective. Use of rFVIIa as a “last-ditch” effort in the absence of conventional treatment is not recommended.¹²⁰

The patient or their next of kin should be advised of the proposed benefit and risks of off-label use of rFVIIa. It is also recommended that hospitals devise a system of review and analysis of all cases of off-label rFVIIa usage.

A recent review provided the following additional points about using rFVIIa.¹²⁷

- For off-label use in the setting of serious bleeding refractory to standard haemostatic therapies, a maximum of two doses may be considered appropriate, with further doses being given only after additional expert consultation.
- The transfusion service or pharmacy should control the use of rFVIIa for release in patients.
- Content experts with experience in haemostasis are appropriate gatekeepers for this type of therapy.
- In some cases, where patients are in remote hospitals without specialists, it could be released under guidance from a specialist via telemedicine or telephone consultation.
- In the situation where rFVIIa must be used for control of life-threatening bleeding in patients who do not respond to other forms of therapy, the use of an international registry (already available for paediatrics, see www.isth.org) should be encouraged. Specialist physicians should be consulted in these situations and

should release the drug on a case-by-case basis, evaluating the total picture and attempting to capture as much data from the treatment as possible.

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Duality of Interest

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