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ORIGINAL ARTICLE

The evidence for the use of recombinant factor VIIa in massive bleeding: development of a transfusion policy framework

C. J. Moltzan,* D. A. Anderson,† J. Callum,‡ S. Fremes,§ H. Hume,¶ C. D. Mazer,**
M. C. Poon,†† G. Rivard,‡‡ S. Rizoli§§ & S. Robinson† **Department of Internal Medicine, St. Boniface General Hospital, Winnipeg, †Department of Internal Medicine, QEII Health Sciences Centre, Halifax, ‡Department of Pathology and Laboratory Medicine, Sunnybrook Health Sciences Centre, Toronto, §Department of Surgery, Sunnybrook Health Sciences Centre, Toronto, ¶Transfusion Medicine, Canadian Blood Services Head Office, Ottawa, **Departments of Physiology, Anesthesia and Critical Care, St. Michael's Hospital, Toronto, ††Department of Medicine, Foothills Hospital, Calgary, ‡‡Department of Pediatrics, Sainte-Justine Hospital, Montreal, and §§Departments of Surgery and Critical Care Medicine, Sunnybrook Health Sciences Centre, Toronto*

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SUMMARY. A review of the recent randomized control trial evidence of the use of recombinant factor VIIa (rFVIIa) in massive bleeding. rFVIIa is a recombinant genetically engineered clotting factor that has been used for the management of haemophilia patients with inhibitors. There has been increasing use in patients with massive bleeding, even when there is no underlying coagulation disorder present. In November 2006, the Canadian National Advisory Committee on Blood and Blood Products engaged in a consultation and review process with several leading Canadian experts to review and discuss the current evidence up to November 2006. There is little evidence to support the routine use of rFVIIa in massive bleeding on review of 13 randomized controlled trials. rFVIIa should only be considered as part of a transfusion policy framework for massive bleeding after all other transfusion and supportive measures are considered. An example of a policy framework is presented.

Key words: massive bleeding (haemorrhage), transfusion protocol, recombinant activated factor VII.

The Canadian National Advisory Committee (NAC) on Blood and Blood Products is an interprovincial medical and technical advisory body to provincial and territorial health ministries. One of its mandates is to provide professional leadership in identifying, designing and implementing cost-effective blood utilization management initiatives for the optimization of patient care.

In November 2006, the Canadian NAC engaged in a consultation process with several leading medical experts to discuss issues regarding the use of recombinant factor VIIa (rFVIIa).

An *ad hoc* subcommittee was established to offer recommendations on the medical and prerequisite conditions for appropriate use of rFVIIa, based on a review of current medical literature, focusing on controlled clinical trials. This paper presents the utilization management recommendations and suggests how they can be applied within a health care system. The intent is to introduce a common policy framework across Canada.

This policy framework involves the elements listed below.

1 A common list of medical and prerequisite conditions for the compassionate use of rFVIIa.
2 A medical screening system by designated physicians with expertise in thrombosis/haemostasis and transfusion medicine for all requests for rFVIIa use within a health region.
3 Standardized information sharing on rFVIIa utilization.
4 An evaluation of the progress and outcome of the rFVIIa Utilization Management Framework in 1-year time.

Correspondence: Dr Catherine Moltzan, Transfusion Services, St Boniface General Hospital, L1 102 – 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6, Canada.
Tel: 204-235-3924; fax: 204-237-6048; e-mail: catherine.moltzan@cancercare.mb.ca

BACKGROUND

Factor VIIa

rFVIIa is recommended in Canada for haemophilia A/B patients with inhibitors to factor VIII or factor IX, respectively, for the treatment of bleeding episodes, including treatment and prevention of those occurring during and after surgery. Novo Nordisk manufactures rFVIIa in Denmark (inside Canada the product is known as NiaStase®, outside Canada the product is marketed as NovoSeven®). rFVIIa at high doses induces haemostasis at the site of injury by forming complexes with exposed tissue factor and by binding to activated platelet surface where it generates thrombin via direct activation of factor X (and of factor IX in non-haemophilia situations) (Hoffman *et al.*, 1998). It is administered intravenously and is dosed according to body weight.

In addition to use for haemophiliacs or patients with acquired inhibitors to FVIII, rFVIIa has been used in various clinical situations:

1 for other haematological indications, i.e. bleeding patients with FVII deficiency, or platelet function defects and
2 to promote clot formation and stop bleeding in life-threatening clinical situations, including trauma, surgery and obstetrics.

rFVIIa is a genetically engineered protein expressed from cloned human FVII genes in baby hamster kidney cells. No material of human origin is used in either the production process or in the final product, thus rFVIIa is less likely than human blood products to transmit infectious agents. However, patients with disseminated intravascular coagulation, advanced atherosclerotic disease, crush injury or septicaemia may have an increased risk of developing thrombotic events in association with rFVIIa treatment.

TREND IN rFVIIa USE

rFVIIa use for non-haemophilia indications is increasing largely based upon a body of case reports, small case series and anecdotal experience demonstrating benefit for reducing bleeding in critically ill patients. However, for most clinical circumstances, there is a lack of adequately powered randomized clinical trials using clinically important end-points to provide evidence to support the effectiveness of the product. In addition, there are significant safety concerns because of the potential thrombotic risks of the product, rFVIIa.

The rFVIIa Medical Task Force, a panel of 11 clinical experts, gathered to review evidence from randomized clinical trials and to reach consensus on rFVIIa for a variety of unlicensed (off-label) use.

Recommendations and conclusions are based on the interpretation of available evidence, and where evidence was lacking, consensus of expert clinical opinion was received. A draft of the rFVIIa framework was circulated to the NAC members for feedback. The results of this process were reviewed by the expert panel and modifications to the draft were made where appropriate.

The literature review identified 13 randomized clinical trials (see Table 1) evaluating the use of rFVIIa for the reduction of bleeding in a variety of clinical scenarios up to November 2006. These studies were reviewed in detail. They are divided into two categories: those that were designed to show a reduction in bleeding (Table 1) and those that were designed to demonstrate decreased blood loss after the onset of bleeding (Table 2).

RANDOMIZED TRIALS OF USE OF FVIIa IN NONHAEMOPHILIAC BLEEDING PATIENTS

Trauma

There were two concurrent randomized control trials (Boffard *et al.*, 2005). One study involved patients with penetrating trauma and the other with blunt trauma. The primary end-point was a reduction in units transfused in 48 h after randomization in patients alive at 48 h. The penetrating study showed no statistical difference in units transfused. The blunt study did demonstrate a 2·6 unit reduction in transfusion favouring the rFVIIa arm. However, when all randomized patients were included (including the patients dying within 48 h), there was no longer a significant benefit of rFVIIa. The data are insufficient at this time to recommend use of rFVIIa in treatment of patients with blunt or penetrating trauma.

Pelvic trauma

A randomized, double-blind, placebo-controlled trial evaluating rFVIIa in reducing perioperative blood loss in patients with normal haemostasis undergoing surgery for repair of major/traumatic pelvic fracture was performed (Raobaikady *et al.*, 2005). The primary end-point was total volume of perioperative blood loss. The blood loss was not significantly different between the two groups, and rFVIIa in the treatment of patients undergoing major pelvic surgery to reduce blood loss is not recommended.

Table 1. Summary of randomized controlled using rFVIIa in active bleeding

Category	References	Indication	Study design	Total sample	Major eligibility criteria	Dosing	Mean age	Primary end-point	Primary results	Statistical significance	Author's study conclusion
Trauma	Boffard *et al.* (2005)	Blunt trauma	Two parallel randomized placebo-controlled, double-blind clinical trial	158	6 RBC units in 4 h, after eighth unit, 1st dose of rFVIIa (given patient would require more units)	200 μg kg^{-1} followed by 2 doses of 100 μg kg^{-1} at 1 and 3 h later or placebo	33 ± 13 years	Units of RBCs transfused within 48 h of first dose of rFVIIa	rFVIIa – reduction of 2·6 RBC units compared with control	$P = 0{\cdot}02$	rFVIIa resulted in a reduction in RBC units transfusions in blunt trauma
	Boffard *et al.* (2005)	Penetrating trauma	As above	143	As above	As above	29 ± 10 years	As above	rFVIIa – reduction of 1 RBC unit compared with control	$P = 0{\cdot}10$	rFVIIa resulted in no significant reduction in RBC units transfusions in penetrating trauma
Cardiac surgery	Diprose *et al.* (2005)	Intractable blood loss after cardiac surgery	Double-blind, randomized placebo-controlled trial	20	Complex non-coronary cardiac surgery	1 dose 90 μg kg^{-1} or placebo after cardiopulmonary bypass	59–76·5	Number of patients receiving any transfusion; total unit of RBC; occurrence of AE	rFVIIa – two patients received 13 units; control – 8 patients received 105 units; group did not differ for AE	Total number of patients transfused ($P = 0{\cdot}037$); total number of units transfused (red cells and coagulation products) ($P = 0{\cdot}011$)	Despite limitations, it was shown that rFVIIa significantly reduces the need for transfusions in complex non-coronary cardiac surgery without causing AE
HSCT	Pihusch *et al.* (2005)	Bleeding post-HSCT	Randomized double-blind placebo-controlled trial	100	Moderate or severe bleeding post-HSCT	7 doses, 40, 80, 160 μg kg^{-1} or placebo	37·5	Change in bleeding score 38 h after first dose	No significant difference		Very heterogeneous group of patients; no significant difference detected
ICH	Mayer *et al.* (2005a)	Acute intracerebral haemorrhage	Double-blind randomized placebo-controlled dose-escalating trial	48	Spontaneous ICH diagnosed by CT within 3 h of symptom onset	A single dose 10,20,40, 80,120 and 160 μg kg^{-1} or placebo	61 ± 15 years	Frequency of adverse events related to (probably, possible) treatment	No noticeable difference in type, frequency or severity of adverse events were observed between dose groups	6 potentially related adverse events, 2 cases of DVT and 2 new onsets of EKG changes	No major safety concerns using the wide range of doses were identified
ICH	Mayer *et al.* (2005b)	Acute intracerebral haemorrhage	Double-blind randomized placebo-controlled trial	400	Spontaneous ICH diagnosed by CT within 3 h of symptom onset	A single dose 40, 80, 160 μg kg^{-1} or placebo	66 ± 12 years	Percentage change in the volume of ICH at 24 h	Increase % growth rFVIIa – 40 μg: 16%; 80 μg: 14%; 160 μg: 11%; control: 29%	40 μg ($P = 0{\cdot}07$); 80 μg ($P = 0{\cdot}05$); 160 μg ($P = 0{\cdot}02$)	Early rFVIIa limits growth of haematoma, reduces mortality and improves functional outcomes, despite small increase in thromboembolic adverse events

Table 1. Continued

Category	References	Indication	Study design	Total sample	Major eligibility criteria	Dosing	Mean age	Primary end-point	Primary results	Statistical significance	Author's study conclusion
Gastrointestinal bleeding	Bosch *et al.* (2004)	Cirrhosis	Randomized double-blind placebo-controlled trial	245	Requiring volume replacement and scheduled for endoscopy within 12 h of admission	8 doses of 100 μg kg^{-1} or placebo	53·4 years	Failure to control UGIB within 24 h Failure to prevent rebleeding between 24 h and day 5 death in 5 days	rFVIIa – 5%; control – 8% rFVIIa – 8%; control – 9% rFVIIa – 6%; Control – 3%	$P = 0{\cdot}31$ $P = 1{\cdot}00$ $P = 0{\cdot}38$	No overall effect of rFVIIa was observed

DVT, deep venous thrombosis; EKG, electrocardiogram.

Cardiovascular surgery

It is a randomized, double-blind, placebo-controlled pilot study evaluating rFVIIa's effect on reducing the need for transfusions in 20 patients undergoing complex non-coronary cardiac surgery requiring cardiopulmonary bypass (Diprose *et al.*, 2005). The study did show a significant benefit in the rFVIIa arm. It also suggested that rFVIIa is safe to use. However, this pilot study was too small and the baseline characteristics of the group was too different from which to draw definite conclusions from. Until these results are confirmed in a large, randomized study using clinically relevant outcomes, the use of rFVIIa is 'investigational' in this setting.

Prostatectomy

A randomized, double-blind, placebo-controlled trial evaluating rFVIIa in reducing perioperative blood loss in 36 patients with normal coagulation system parameters undergoing prostatectomy was performed (Friederich *et al.*, 2003). There was a reduction in perioperative blood loss in the rFVIIa group; however, it was noted that the control arm had an unexplainable high blood loss. This small pilot study has not been confirmed by a larger follow-up trial. This study did not demonstrate sufficient evidence to recommend use of rFVIIa in patients undergoing prostatectomy at this time.

Haematopoietic stem cell transplantation

Haematopoietic stem cell transplantation (HSCT) is a multicentred, randomized, double-blind, placebo-controlled trial evaluating the effect of rFVIIa in the treatment of bleeding complications following HSCT (Pihusch *et al.*, 2005). The primary end-point was the change in bleeding scores between the first administration of rFVIIa and 38 h later. This study demonstrated there was no significant effect or change in the bleeding score in comparison to placebo regardless of the dose of rFVIIa used. The use of rFVIIa in the treatment of bleeding complications following HSCT is not recommended.

Intracranial haemorrhage

There were three randomized, double-blind, placebo-controlled trials assessing the use of rFVIIa in intracranial haemorrhage (ICH) and (1) the frequency of adverse events, (2) the reduction of haematoma growth after ICH and (3) the outcomes at day 90. Studies involved ICH diagnosed within 3 h of symptom

Table 2. Summary of the randomized controlled trials using rFVIIa to prevent bleeding

Category	References	Indication	Study design	Total sample	Major eligibility criteria	Dosing	Mean age	Primary end-point	Primary results	Statistical significance	Author's study conclusion
Trauma	Raobaikady *et al.* (2005)	Traumatic pelvic fracture	Double-blind, randomized placebo-controlled trial	48	Potential blood loss of 50% for major pelvic fracture caused by trauma during semielective surgery	90 μg kg^{-1} or placebo at first skin cut with potential second identical dose 2 h later	44	Total volume of perioperative blood loss	Total volume: rFVIIa – 2070 mL; control –1534 mL	$P = 0{\cdot}79$	No significant difference in total volume of perioperative blood loss between rFVIIa and placebo
Prostatectomy	Friederich *et al.* (2003)	Retropubic prostatectomy	Randomized double-blind placebo-controlled trial	36	Scheduled to undergo major prostatectomy surgery	20, 40 μg kg^{-1} or placebo early in the operative phase	62·7	Safety and efficacy in terms of reduction of perioperative blood loss and transfusion requirements	Blood loss: rFVIIa – 20 μg, 1235mL; 40 μg, 1089 mL; control, 2688 mL	$P = 0{\cdot}001$	Treatment of patients undergoing surgery associated with large blood loss with rFVIIa seems effective and safe
GI	Lodge *et al.* (2005a)	Liver resection	Double-blind, randomized placebo-controlled trial	204	Non-cirrhotic adults scheduled to undergo partial hepatectomy (if surgery time exceeds 6 h)	20 and 80 μg kg^{-1} or placebo and a repeat dose if surgery beyond 6 h	56·5 years	Patients requiring RBC transfusion during or the 48-h period after surgery	Portion of patients who required RBC and mean RBC requirement: rFVIIa – 20 μg, 41%, 1354 mL; 80 μg, 25%, 1036 mL; control – 37%, 1024 mL	% of patients: $P = 0{\cdot}09$; RBCs required $P = 0{\cdot}78$	Did not result in a statistical reduction in either the number of patients transfused or volume of blood products administration
	Shao *et al.* (2006)	Partial hepatectomy	Randomized double-blind, parallel group, placebo-controlled trial	235	Cirrhotic adults scheduled for partial hepatectomy	50 and 100 μg kg^{-1} or placebo 10 min prior to first cut and q 2 h until end of surgery	48·5–54·1 years	Patients receiving RBC transfusions and the amount of RBCs transfused during surgery and the first 48-h postsurgery	Portion of patients who required RBCs: rFVIIa – 50 μg kg^{-1}, 51%; 100 μg kg^{-1}, 36%; control – 38%	% of patients requiring RBCs: $P = 0{\cdot}59$; amount of RBCs transfused: $P = 0{\cdot}68$	No statistically significant effect on efficacy end-points was observed
	Planinsic *et al.* (2005)	Orthotopic liver transplant	Multicentre, double-blind, randomized placebo-controlled, exploratory trial	87	End-stage liver disease undergoing OLT	Single dose of 20, 40 and 80 μg kg^{-1} or placebo within 10 min of first cut	50 years	Total number of RBC units transfused during the perioperative period	No difference in the perioperative RBC requirements between placebo and rFVIIa	No significant difference ($P > 0{\cdot}05$) in transfusion requirements	The doses studied did not have any effect on the number of RBC transfusions required

Table 2. Continued

Category	References	Indication	Study design	Total sample	Major eligibility criteria	Dosing	Mean age	Primary end-point	Primary results	Statistical significance	Author's study conclusion
	Lodge *et al.* (2005b)	Orthotopic liver transplant	Multicentre, randomized double-blind, placebo-controlled, exploratory trial	209	Scheduled to undergo OLT because of cirrhosis	Repeated doses 60 and 120 μg kg^{-1} or placebo. First dose 10 min of skin cut, then q 2 h, until final dose at closure	52·7 years	Total number of RBC units transfused during the perioperative period	No significant effect of rFVIIa was observed	No statistical difference ($P >$ 0·05) was found for any parameter of transfusion requirement	rFVIIa treatment did not show a significant effect on the number of RBC transfusions required during OLT

onset. The primary end-point for the dose-escalating trial was the frequency of adverse events related (probable, possible) to rFVIIa (Mayer *et al.*, 2005a). The dose-escalating trial evaluated a wide range of rFVIIa doses in acute ICH with six adverse events considered possibly treatment related.

The primary end-point in the second trial reviewed was percentage change in the volume of ICH at 24 h (Mayer *et al.*, 2005b). This trial showed that the haematoma volume increased more in the placebo arm than in the rFVIIa groups. In summary, this was a phase II study showing that rFVIIa limits growth of haematoma formation. However, there is also an increased risk of adverse thrombotic events.

This phase II study had lead to the performance of a larger phase III study. The larger phase III trial results (unpublished at this time), which were presented at the 2007th European Stroke Conference in Glasgow, UK concluded this to be a negative study (Mayer *et al.*, 2007). Although the results demonstrated improvement in clinical outcomes in terms of functional independence and neurological impairment on day 15, the bleeding, mortality and severe disability was not improved at the end of the study period (day 90). As mortality and severe disability at day 90 was the primary end-point of the study, rFVIIa in the treatment of patients with ICH is not recommended.

Liver resection

There were two randomized, double-blind, placebo-controlled trials to evaluate the haemostatic effect and safety of rFVIIa in major partial hepatectomy (Lodge *et al.*, 2005a; Shao *et al.*, 2006). Both studies showed that the proportion of patients who required perioperative red blood cell (RBC) transfusion was similar in all three groups. As the dosing of rFVIIa in both studies did not result in a statistically significant reduction in either the number of patients transfused or the volume of blood products administered, rFVIIa use in the treatment of patients undergoing surgery for liver resection is not recommended.

Liver transplant

Two multicentred, randomized, double-blind, placebo-controlled exploratory trials were reviewed evaluating the effect of rFVIIa in the reduction of bleeding and reducing transfusion required by patients undergoing orthotopic liver transplantation (OLT) (Lodge *et al.*, 2005b; Planinsic *et al.*, 2005). There were no significant differences in required RBC units between placebo and rFVIIa in either study. rFVIIa use to

Table 3. rFVIIa screening framework and dosing specifications

Massive intractable bleeding

Transfused ≥8 units RBC in 24 h or >4 units PRBC in first hour of resuscitation in the presence of ongoing uncontrollable bleeding

Recommended dosage: rFVIIa should be dosed (rounded) to nearest vial to avoid wastage

Recommended initial dose: 20–50 μg kg^{-1} – this may be repeated in 30 min if bleeding does not stop. A third dose may be given up to2 h later for continued bleeding (maximum three doses). Round to nearest vial (i.e. 1·2, 2·4, 3·6, 4·8 mg vials)

Adequate haemostatic measures should be taken before requesting rFVIIa

The dosage recommended is a consensus expert opinion based on

Lack of dose response effect where dose finding/escalation was incorporated into some of the trials. In the ICH trial, higher doses appear not to have additional benefit, but with increase in arterial thrombotic events

In trials using high dose only, there is no documentation of the rationale why the high doses were used

Consideration of potential adverse events with high dosing (Chhina *et al.*, 2004; O'Connell *et al.*, 2006)

Reports of efficacy with low dose rFVIIa in cardiac surgery and percutaneous liver biopsies (Carvalho *et al.*, 2002; Romagnoli *et al.*, 2006)

Small doses of rFVIIa normalize thrombin generation in subjects with FVII deficiency (Brummel Ziedens *et al.*, 2004)

Administration

rFVIIa is dosed according to body weight. rFVIIa should not be mixed with infusion solutions and should be administered IV direct over 2–5 min. Reconstituted solution should be used within 3 h

Haemostatic and other measures to be taken for massive intractable bleeding prior to requesting rFVIIa

Attempt to correct the coagulopathy with frozen plasma (15 mL kg^{-1}) if the aPTT is >1·5× normal or the PT, measured as the INR, is greater than 1·5. rFVIIa dramatically shortens the PT and therefore after administration of rFVIIa, additional plasma should be administered to maintain the aPTT <1·5× normal

Platelet transfusions (1 pool) should be administered to target the platelet count

$>100 \times 10^9$ L^{-1} for head trauma or neurosurgery

$> 50 \times 10^9$ L^{-1} for all other patients

In cardiac surgery, renal or hepatic dysfunction, platelet dysfunction can cause significant bleeding even with normal platelet counts and platelet transfusions may be appropriate

These values are not absolute and should be considered minimum standard. There may be circumstances where targeting a platelet count of 75×10^9 L^{-1} is appropriate to ensure that a minimum platelet count of 50×10^9 L^{-1} is maintained at all times. Platelets are very important for the efficacy of rFVIIa

Cryoprecipitate (1 unit/5–10 kg or 15 mL/5–10 kg) should be administered to maintain fibrinogen >1·0 g L^{-1}

A fibrinogen level should be obtained first before the use of cryoprecipitate (Initial routine blood work [for massive bleeds] should include PT/INR, aPTT and fibrinogen). Recommended to check fibrinogen levels, PT/INR and aPTT frequently and replace with frozen plasma, cryoprecipitate and platelets based on the results when available

Maintain haemoglobin >80 g L^{-1} in order to optimize haemostasis

Correct acidosis where pH ≤7·1 (Meng *et al.*, 2003)

Calcium replacement should be considered if ionized calcium is below local reference values (Dickerson *et al.*, 2005; Vivien *et al.*, 2005; Fukuda *et al.*, 2006). The best replacement is IV calcium chloride (greatest amount of elemental calcium)

Correct hypothermia if present. This should include patient warming and the warming of intravenous fluids and blood products where appropriate (Wolberg *et al.*, 2004)

Additional measures

There are potential increased risks of arterial and venous thromboembolic events (history of arterial/venous thromboembolism, hereditary thrombophilia, vascular grafts, mechanical heart values, DIC/sepsis, endotoxaemia, atherosclerosis, sickle cell, age >65). These patients have generally been excluded from published clinical trials

Avoid the use of rFVIIa in refractory acidosis (persistent pH <7·1)

aPTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time.

reduce bleeding in patients undergoing OLT is not recommended.

Cirrhosis

A randomized, double-blind, placebo-controlled trial evaluating rFVIIa in controlling upper gastrointestinal bleeding (UGIB) in patients with cirrhosis when administered as an add-on to standard therapy (Bosch *et al.*, 2004). Overall, no effect was observed on the control of primary UGIB, the rate of rebleeding or mortality. rFVIIa use in the treatment of UGIB in patients with cirrhosis is not recommended.

REVIEWERS' CONCLUSIONS OF THE RANDOMIZED CLINICAL RESEARCH TRIALS WITH rFVIIa

Caution needs to be exercised in interpreting the results of available studies with rFVIIa. Most studies were small dose-finding studies that used reduction in blood loss or need for transfusion as the primary end-point. Studies were too small to be powered to show differences in clinically important end-points such as mortality or major morbidity. Studies were also too small to show estimates of risk of major thromboembolic complications with rFVIIa.

Until large adequately powered clinical trials are available that demonstrates the benefit of rFVIIa in reducing rates of clinically important end-points with acceptable risk, the routine use of rFVIIa for such indications cannot be recommended. This is in concordance with a recent Cochrane database review on the topic (Stanworth *et al.*, 2007). It is also important that data surrounding its use are collected and analysed in these situations because some of these clinical situations will not be amenable to large randomized controlled trials.

INCORPORATION OF rFVIIa INTO A TRANSFUSION POLICY FRAMEWORK

The Canadian NAC rFVIIa Medical Task Force has developed recommendations to assist physicians in screening requests for rFVIIa for massive bleeding. These recommendations are as follows, as discussed below and in Table 3.

1 rFVIIa should be used under the direction of a physician or physicians experienced in its use. This is done for three reasons:

   (a) to ensure that all other measures to achieve haemostasis have been taken;
   (b) to ensure proper dosing and administration of rFVIIa; and
   (c) to ensure the collection of outcome data and adverse event data. [The latter point is very important because this may be the only way that such information can be collected in a systematic manner.]

2 Because of the paucity of published evidence, the potential for harm in some clinical situations and the lack of cost/benefit data, rFVIIa should be used only in the following clinical situations:

   (a) where randomized, controlled clinical trials have shown reasonable efficacy with reasonable risks/costs; or
   (b) where a sound rationale for the product's use can be provided
   (c) the risks are clearly understood by the administering clinician; and
   (d) the product is administered properly.

3 The specific medical screening questions and dosing recommendations for unlicensed use of rFVIIa use are attached. The recommendations are intended to allow health care providers to deal with "compassionate" requests for rFVIIa, some of which may be valid, some of which may not.

4 These recommendations will be reviewed and revised as new peer-reviewed, clinical trial information becomes available.

CONCLUSION

rFVIIa has been used in the management of patients with massive bleeding. However, at the current time the use of rFVIIa should be considered on a case-by-case basis where other haemostatic measures have been taken first. The evidence reviewed in this paper does not support the routine use of rFVIIa in massive bleeding. However, there will still be circumstances where the addition of rFVIIa may be necessary in the management of an individual patient. Therefore, it is important to incorporate the requests for rFVIIa into a framework that ensures that other haemostatic measures have been taken.

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