

Recombinant Activated Factor VII in Obstetric Hemorrhage: Experiences from the Australian and New Zealand Haemostasis Registry

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OBJECTIVE: Through the Australian and New Zealand Haemostasis Registry, we report on the Australian and New Zealand experience with recombinant activated factor VII (rFVIIa) in obstetric patients.

METHODS: The role of rFVIIa for off-label indications, including trauma, cardiac surgery, and severe postpartum hemorrhage, remains controversial. The Haemostasis Registry established by Monash University in Melbourne, Australia monitors off-label use of rFVIIa across Australia and New Zealand. The purpose of this study was to summarize Registry data for all obstetric hemorrhage patients treated with rFVIIa at participating hospitals between January 2002 and July 2008. The primary outcome measures were reduction or cessation of bleeding (positive therapeutic response), mortality, and hysterectomy rate.

RESULTS: During the study period, the Registry received data for 2128 patients. This included 110 cases of administration of rFVIIa in obstetric patients from 38 hospitals, comprising 5% of the total Registry population, 105 of whom were treated for acute hemorrhage. Women received median (interquartile range) individual doses of 92 $\mu\text{g}/\text{kg}$ (73–100) of rFVIIa (median total dose 92 $\mu\text{g}/\text{kg}$ [58–108]), and 78% of patients received a single dose. The positive response rate to rFVIIa was 76% with 64% responding to the first dose. Ninety-one percent of women were alive at 28 days. Forty-three women (41%) underwent hysterectomy before receiving rFVIIa and, of those remaining, 13 (21%) required hysterectomy after rFVIIa therapy. Two thromboembolic events (1 pulmonary embolism and 1 deep venous thrombosis) and 1 case of hypoxic-ischemic encephalopathy resulting from severe anoxia were reported.

CONCLUSIONS: The reported effect of rFVIIa in many, but not all, obstetric cases was positive. There was no mortality as a result of thromboembolic complications. Randomized, controlled trials are required to confirm its safety and efficacy and to assess the possibility that use at an earlier stage in treatment of severe postpartum hemorrhage may avoid the need to resort to postpartum hysterectomy for control of bleeding, thus preserving fertility.

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Severe postpartum hemorrhage (PPH) is often unpredictable and catastrophic and remains a leading cause of maternal morbidity and mortality in developing countries.^{1,2} The Australian Institute for Health and Welfare reported that hemorrhage accounted for

28% of direct maternal deaths in the period 2000–2002.³ The incidence and the severity of obstetric hemorrhage seems to be increasing in Western countries.⁴ In a population-based study in Australia, the proportion of women with PPH who received a blood transfusion increased from 2% in 1994 to 12% in 2002.⁵ In another

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Australian study, the incidence of hysterectomy resulting from PPH increased from 0.03% in 1999 to 0.08% in 2002.⁶ One reason for the observed increase in severe obstetric hemorrhage may be an increase in placenta accreta after prior cesarean delivery,⁷⁻¹⁰ but there is also an increase in PPH after vaginal birth.¹¹

Severe blood loss can occur rapidly after delivery and often goes unrecognized.¹² Not only do health professionals frequently underestimate the degree of blood loss,¹³ but otherwise healthy women can withstand substantial blood loss before developing clinical symptoms and signs of shock. Initial steps to control bleeding include uterotonic medications and uterine massage or compression and blood component therapy, followed by surgical interventions such as internal iliac artery ligation, or uterine artery embolization. Peripartum hysterectomy is usually reserved as the therapy of last resort.

New treatments that could reduce maternal mortality and morbidity resulting from major obstetric hemorrhage would be welcomed but the effects of such treatment must be examined for safety and efficacy, especially in comparison to current therapeutic interventions.

Recombinant activated factor VII (rFVIIa) was developed for prevention or treatment of bleeding in hemophilia patients who have inhibitors to factor VIII and factor IX.¹⁴⁻¹⁶ Licensed in many countries for this indication, it acts by enhancing coagulation at the site of bleeding by triggering and augmenting the thrombin burst, ultimately leading to formation of a stable fibrin clot.^{17,18}

Numerous case reports and case series describe the off-label use of rFVIIa¹⁹⁻²¹ including situations such as PPH²¹⁻²⁸ and trauma.²⁹ Although questions relating to the role of rFVIIa in preserving fertility or reducing maternal morbidity or mortality can only be answered by a randomized, controlled trial, analysis of Registry data may provide information relating to the current clinical use of rFVIIa in obstetrics and could help identify major trends in outcome or adverse events and provide hypotheses generating future studies. The Australian and New Zealand Haemostasis Registry (ANZHR) was developed to capture safety and efficacy data of the increasing off-label use of rFVIIa, including use in obstetric hemorrhage. In this article, we report on the cohort of obstetric cases from the ANZHR for the period January 2002 to July 2008 from institutions across Australia and New Zealand, including 27 obstetric cases from the initial report from the Registry.³⁰

METHODS

The ANZHR is a comprehensive registry documenting off-label use of rFVIIa (NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) in patients who do not have hemophilia at participating hospitals throughout Australia and New Zealand.³⁰⁻³³ The Registry was

established by Monash University's Department of Epidemiology and Preventive Medicine supported by an unrestricted educational grant from Novo Nordisk Pharmaceuticals Pty. Ltd. Novo Nordisk had no role in the collection, analysis, and interpretation of data, in writing the report, or in the decision to submit the article for publication.

The ANZHR began receiving data in May 2005 but includes retrospective cases dating back to 2000, with the first use in obstetric hemorrhage reported in 2002. More than 90 hospitals from New Zealand and all States and Territories of Australia currently contribute data to the Registry. We estimate that this represents approximately 50% of hospitals in Australia and New Zealand using rFVIIa, but these hospitals represent in excess of 83% of rFVIIa doses administered in the region. Submitting hospitals are required to commit to supplying complete datasets. This commitment, audited by the Department of Epidemiology and Preventive Medicine, limits bias and prevents the reporting of only positive experiences.

Participating institutions have obtained approval from local Ethics Committees to collect deidentified information without patient consent for inclusion in the ANZHR. This report includes all patients who received rFVIIa as part of treatment for PPH.

Standardized data forms were completed by trained ANZHR coordinators at each center from patient medical records. Inquiries to treating clinicians are made by data collectors when necessary, for example, if the patient medical record does not include documentation regarding the effect of rFVIIa on bleeding. Copies of ANZHR data collection forms and the Data Dictionary are available at www.med.monash.edu.au/epidemiology/traumaepi/hemostasis.html. Transfusion information was collected for the 24 h preceding and after each dose of rFVIIa and laboratory test results were collected for the closest tests taken before and after each dose of rFVIIa. Data collection included asking prescribing clinicians to define "responders" as patients in whom bleeding had stopped or decreased and "nonresponders" as those in whom bleeding was unchanged or had increased after each dose of rFVIIa. All adverse events (cerebrovascular accident, transient ischemic attack, deep vein thrombosis [DVT], pulmonary embolism, acute myocardial infarction, arterial thrombosis, other thrombotic events, disseminated intravascular coagulation, multiorgan failure, acute respiratory distress syndrome, allergic reaction, and other nonthrombotic adverse events) during the patient's hospital stay up to a maximum of 28 days after treatment with rFVIIa were reported with the clinician's assessment of the likelihood that these events were linked to the administration of rFVIIa by assigning 1 of the following relationships: not linked, unlikely to be linked, possibly linked, probably linked, or definitely linked.

Table 1. Primary Obstetric Cause of Hemorrhage for Cases Received by the Australian and New Zealand Haemostasis Registry

	No. (%) of patients	No. of deaths
Total ^a	105 (100)	9
Uterine atony	19 (18)	1
Uterine rupture	3 (3)	
Placenta accreta/percreta	17 (16)	
Placental abruption	9 (9)	1
Placenta previa	13 (12)	2
Preeclampsia/eclampsia	6 (6)	1
Intrauterine fetal death	9 (9)	1
Acute fatty liver of pregnancy	3 (3)	
Amniotic fluid embolism	3 (3)	1
Retained products of conception	4 (4)	
Obstetric injury	4 (4)	
No identifiable cause of hemorrhage	5 (5)	
Other ^b	10 (10)	2

^a Five cases excluded where use of recombinant activated factor VII (rFVIIa) was for prophylaxis.

^b Includes aortic dissection (1), severe Systemic Lupus Erythematosus and thrombophilia (1), sepsis (1), splenic artery aneurysm (1), bladder rupture (1), cord prolapse (1), broad ligament hematoma (1), uterine fibroids (1), congenital macrothrombocytopenia (1), pulseless electrical activity due to pulmonary embolus (1).

Statistical Analysis

Nonparametric statistics were used throughout for consistency of reporting and analysis because the vast majority of measured variables did not conform to normal distributions. Blood products before and after rFVIIa dose were compared in individuals using Wilcoxon's matched-pairs signed rank tests. The relationship between categorical measurements and the outcomes of interest, response, and mortality were assessed using the χ^2 test or Fisher's exact test. Variables were categorized as follows: maternal age (15–24/25–34/35–44/>44 yr), weight ($\leq 60/61–80/>80$ kg), dose ($\leq 80/81–100/>100$ $\mu\text{g}/\text{kg}$), temperature ($<35.0/35.0–36.5/36.6–37.5/>37.5^\circ\text{C}$), pH ($<7.20/7.20–7.35/>7.35$), hemoglobin ($\leq 7.0/7.1–8.0/8.1–9.0/9.1–10.0/>10.0$ g/dL), hematocrit ($\leq 20/21–25/26–30/>30\%$), platelet count ($\leq 50/51–70/71–90/>90 \times 10^9/\text{L}$), fibrinogen levels ($\leq 1.0/1.1–1.5/1.6–2.0/>2.0$ g/L), international normalized ratio ($\leq 1.5/>1.5$), activated partial thromboplastin time ($\leq 45/46–90/>90$ s), obstetric presentation type (Table 1), hysterectomy (none/before rFVIIa/after rFVIIa), number of packed red blood cells (PRBCs), fresh frozen plasma (FFP), cryoprecipitate, and platelet units (none/1–5/6–10/11–15/16–20/21–25/>25 U), before rFVIIa administration, interval from bleeding onset to drug administration ($<2.0/2.0–4.9/5.0–10.0/>10.0$ h), and patient location at time of rFVIIa administration (operating room/intensive care unit (ICU)/delivery suite). $P < 0.05$ was considered statistically significant. All analyses were conducted using Stata v. 9.2 (Stata Corp., College Station, TX).

RESULTS

As of July 25, 2008, the ANZHR had collected data for 2128 cases, including 110 patients from 38 hospitals where rFVIIa was used in obstetric patients. This included 27 obstetric patients reported previously.³⁰ Data were collected from the patient medical record >2 mo after treatment for 73 cases. The number of cases per hospital was 1–10, and patients ranged from 17 to 48 yr of age with a mean ($\pm\text{SD}$) of 32 (± 6) yr. The use of rFVIIa in obstetrics has steadily increased since 2002 (2 cases) and peaked in 2007 with 35 cases.

Five patients received rFVIIa prophylactically before delivery. Four of these were women with known factor VII deficiency and the fifth was a woman with coagulopathy due to acute fatty liver of pregnancy who required emergency cesarean delivery. These cases have been excluded from further analyses presented in this article.

A variety of obstetric conditions formed the underlying primary cause of bleeding (Table 1). All women received rFVIIa after delivery.

Efficacy was assessed after each individual dose and also as a final response after the final dose. Efficacy assessment could not be reported in all cases, particularly where data were collected retrospectively. Decrease or cessation of bleeding was observed in 64% of cases after the first doses when efficacy was reported (94 cases). In 71 of the 94 cases (76%), rFVIIa was considered to have decreased or stopped bleeding after the final dose of rFVIIa.

The 105 patients received 136 doses of rFVIIa. One patient received 4 consecutive doses and 82 patients (78%) received a single dose of rFVIIa. The median dose was 92 $\mu\text{g}/\text{kg}$ (interquartile range, 73–100; range, 9–139), and the median total dose was 92 $\mu\text{g}/\text{kg}$ (interquartile range, 58–108; range, 9–273).

The patient who received 4 doses had an emergency hysterectomy for uterine rupture presenting as circulatory collapse with delivery of a stillborn baby at 39 wk gestation. Four doses, each of 9.6 mg, were given over a 14-h period with the initial dose given in the operating room at the time of the hysterectomy. A second dose was given before the patient was transferred to the angiography suite for embolization of the right internal iliac artery. She returned to the operating room for evacuation of blood and clots, a right oophorectomy, and packing but no surgical bleeding site was identified. A third rFVIIa dose was given on return to the ICU. No reduction in bleeding was recorded with these first 3 doses despite continued transfusion of blood products, but bleeding slowly decreased after a fourth dose. In this case, as in all cases with multiple doses, responses were recorded separately for each dose (in this case, unchanged for the first 3 doses and decreased for the fourth dose). The final response was considered to have been positive.

Table 2. Blood Product Usage in the 24 h Before and After Administration of the Initial Dose of Recombinant Activated Factor VII (rFVIIa)

Blood product, units received	PRBC, no. cases (%)		FFP, no. cases (%)		Cryoprecipitate, no. cases (%)		Platelet concentrate, no. cases (%)	
	Before	After	Before	After	Before	After	Before	After
None	6 (6%)	29 (28%)	7 (7%)	59 (56%)	37 (35%)	70 (67%)	26 (25%)	49 (47%)
1–5	12 (11%)	51 (49%)	29 (28%)	30 (29%)	18 (17%)	15 (14%)	65 (62%)	45 (43%)
6–10	28 (27%)	16 (15%)	49 (47%)	9 (9%)	32 (31%)	13 (12%)	9 (9%)	8 (8%)
11–15	28 (27%)	4 (4%)	12 (11%)	5 (5%)	7 (7%)	1 (1%)	1 (1%)	3 (3%)
16–20	19 (18%)	0 (0%)	6 (6%)	1 (1%)	6 (6%)	5 (5%)	3 (3%)	0 (0%)
21–25	4 (4%)	3 (3%)	1 (1%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)
>25	8 (8%)	2 (2%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	0 (0%)
Median (IQR)	11 (8–16)	2 (0–5)	8 (4–11)	0 (0–4)	4 (0–10)	0 (0–4)	2 (1–3)	1 (0–2)
P*	P < 0.001		P < 0.001		P = 0.001		P = 0.003	

PRBC = packed red blood cells; FFP = fresh frozen plasma; IQR = interquartile range.

* Wilcoxon matched-pairs signed-Rank test of individual values before and after rFVIIa.

Details of blood products received are included in Table 2. The majority of patients (83%) received >5 U of PRBCs before administration of rFVIIa. Six patients (6%) received no units of PRBC before rFVIIa: 3 of these patients refused blood transfusion, and 1 was transfused with other blood components before rFVIIa administration and received PRBCs after the dose. The remaining 2 patients were treated with rFVIIa soon after the hemorrhage was recognized and received blood products soon after the rFVIIa dose. rFVIIa treatment was considered to be effective in 3 of the cases (one of the patients refusing transfusion, the patient receiving other blood component therapy, and 1 of those transfused with PRBCs soon after rFVIIa dose).

After the administration of rFVIIa, most patients (76%) received <6 U of PRBCs including 28 patients (27%) who received no further PRBCs. Patterns of use of FFP, cryoprecipitate, and platelet concentrates were similar to those of PRBCs with volumes transfused after rFVIIa administration significantly less than before rFVIIa in individuals for all blood products.

pH data were unavailable for 35 patients at the time of initial rFVIIa administration. Of the remaining 70 patients, 52 (74%) were acidemic (pH <7.35) at the time of the initial rFVIIa dose and 24 (34%) were severely acidemic (pH <7.2). Temperature was not recorded for 24 patients at the time of initial rFVIIa dose. Fourteen of the remaining patients (17%) were moderately hypothermic (temperature ≤35°C), and only 1 patient was severely hypothermic (temperature ≤32°C).

Fifty-six patients (53%) underwent hysterectomy, 43 patients (41%) had hysterectomy before receiving rFVIIa. Of the patients who did not have hysterectomy before receiving rFVIIa (62 patients, 59%), 13 (21%) required hysterectomy after treatment with rFVIIa.

The mortality at 28 days was 9% (n = 9). Two deaths occurred in women with onset of bleeding in very remote localities, and it is likely that delay in reaching medical aid contributed to their deaths. Five deaths (including one of those above) occurred within

Table 3. Details of Adverse Events within 28 d of Administration of Recombinant Activated Factor VII (rFVIIa)

Type of adverse events	Number of adverse events
Cerebrovascular accident	1
Deep vein thrombosis	1
Pulmonary embolism	1
Disseminated intravascular coagulopathy	8
Multiorgan failure	7
Acute respiratory distress syndrome	3
Other ^a	18
Total	39

^a reactive thrombocytosis (1), ileus (1), hypodensities of liver and spleen (1), pelvic hematoma (1), hyperbilirubinemia (1), hypertension (2), superficial thrombophlebitis (1), mild peripheral edema (1), rebleeding (1), pleural effusion (1), abdominal pain (1), small troponin rise (1), cecal perforation (1), peripartum cardiomyopathy (1), neurogenic leg pain (1), systemic inflammatory response syndrome (1), left lung collapse (1).

8 h of rFVIIa administration, all as a direct result of the underlying condition or exsanguination. The remaining 4 patients died at 3, 3, 4, and 17 days after rFVIIa administration, as a result of complications arising from their condition. Causes of death in these 4 patients were listed, respectively, as: multisystem failure after emergency pulmonary embolectomy (before rFVIIa administration) 9 days postpartum, multisystem failure and severe neurological injury following severe disseminated intravascular coagulation (possibly due to amniotic fluid embolism), hypoxic cerebral event due to prolonged hypotension as a result of amniotic fluid embolism, and multisystem failure secondary to eclampsia and thrombotic thrombocytopenic purpura, the latter in one of the patients from a remote community.

Thirty-six nonthromboembolic adverse events were reported in 29 patients (28%) within 28 days of receiving rFVIIa (Table 3). All of these were considered to be either unlikely or not linked to the administration of rFVIIa.

Two patients had nonfatal thromboembolic events (1 pulmonary embolus and 1 DVT), and one patient had hypoxic-ischemic encephalopathy after prolonged

cardiopulmonary resuscitation (CPR). The DVT occurred in a 20-yr-old patient who required an emergency cesarean delivery at term complicated by massive hemorrhage after a failed trial of instrumental delivery. The patient received blood products and rFVIIa (9.6 mg = 117 μ g/kg) with no effect and continued on to peripartum hysterectomy. After transfer to a major metropolitan hospital for intensive care, she returned to the referring maternity hospital on the fifth postpartum day. A left-sided lower extremity DVT was diagnosed and treated, and the patient was discharged to home on postpartum day 9.

The second patient was a 29-yr-old woman with catastrophic hemorrhage due to amniotic fluid embolism presenting as hemodynamic collapse in the second stage of labor. Maternal resuscitation commenced, and emergency forceps delivery was performed approximately 10 min after the initial event with delivery of a live infant. Shortly after delivery, the patient had massive PPH coinciding with manual removal of the placenta. The patient became unresponsive with no pulse or respiration. CPR was commenced, and the patient was transferred to the operating room for hysterectomy and right salpingo-oophorectomy. Recombinant rFVIIa (7.2 mg = 90 μ g/kg) was given after transfusion of 11 U of PRBCs, 0.6 U FFP, 1 U platelet concentrate, and no cryoprecipitate, with minimal effect on bleeding. The patient underwent prolonged CPR and had periods of sustained, profound hypotension and was transferred to the ICU where she was eventually stabilized. Four days later, magnetic resonance imaging of the brain confirmed extensive areas of restricted diffusion affecting the cortex of frontal, parietal, and temporal lobes, changes consistent with hypoxic-ischemic encephalopathy resulting from severe anoxia.³⁴ The patient had persistent severe neurological deficit and was discharged to a rehabilitation facility 13 days postpartum.

The third serious complication was bilateral pulmonary embolism. A multigravid woman received rFVIIa (9.6 mg = 99 μ g/kg) after she had a major hemorrhage into a broad ligament tear at the time of her third cesarean delivery. Bleeding continued into a large broad ligament hematoma (15 \times 15 \times 10 cm), and she remained hemodynamically unstable with arterial blood pressure 58/32 mm Hg and hemoglobin of 6.1 mg/dL. Administration of rFVIIa coincided with an immediate improvement in her arterial blood pressure to 113/85 mm Hg. Ten units of PRBCs and 2 U of FFP were transfused. Six days postpartum, she developed symptoms suggestive of hematoma infection and then became hypoxemic. A computed tomography pulmonary angiogram confirmed bilateral pulmonary emboli, and she was cautiously anticoagulated with IV heparin, followed by warfarin. Her subsequent recovery was uncomplicated.

Low pH (pH \leq 7.2, $P = 0.001$) and low temperature (temperature \leq 35°C, $P = 0.01$) at the time of rFVIIa administration were associated with a lower response

rate. Low pH was also associated with mortality (pH \leq 7.2, $P = 0.01$). Age, weight, rFVIIa dose, PRBC units transfused before rFVIIa and pretransfusion hemoglobin, hematocrit, prothrombin time/international normalized ratio, activated partial thromboplastin time, platelet count, and fibrinogen level were not associated with response to treatment or mortality. The number of doses was not associated with mortality.

DISCUSSION

Obstetric hemorrhage is a life-threatening complication and a leading cause of maternal death. Standard of care includes obstetric interventions for uterine atony, examination for retained or adherent placenta and genital tract trauma, restoration of circulating blood volume and correction of coagulopathy, and appropriate surgical or radiological interventions. Although there are no randomized trial data to inform the appropriate use or timing of rFVIIa in the treatment pathway for obstetric hemorrhage, it is increasingly being used. The role of rFVIIa in the context of life-threatening obstetric hemorrhage and also its potential use before hysterectomy to preserve fertility should be assessed in a randomized, controlled trial. Until the results of such a clinical trial are available, registries such as the ANZHR have the potential to provide continuing data relating to use of rFVIIa in this difficult clinical situation.

This study is one of the largest reported case series of rFVIIa use in PPH. Although the absence of a control group and heterogeneity of bleeding contexts limits the conclusions that can be drawn from this large series, the strength of this dataset is an obligation of participating hospitals to provide complete patient capture, thus avoiding bias from selective case reporting. Despite institutional variability and the absence of a standardized protocol guiding timing of rFVIIa administration, prescribing clinicians reported that rFVIIa was effective in stopping or slowing bleeding in 76% of patients with severe PPH and was also associated with a reduction in blood product use after administration. It should be noted, however, that this outcome measure (response) is a subjective judgment made by the treating clinician and is 1 of the limitations of this study.

In 2007, the United Kingdom Obstetric Surveillance System on peripartum hysterectomy³⁵ reported 28 women having received rFVIIa before hysterectomy. No dosage information is available and, as the authors acknowledge, the United Kingdom Obstetric Surveillance System can only report on failures of rFVIIa and does not collect data on cases in which use of rFVIIa may have avoided hysterectomy.

The majority of the published obstetric cases report successful control of hemorrhage through the use of rFVIIa and consequent high survival rates. Relatively few reports^{25,27,36-38} include patients in whom obstetric bleeding was not successfully controlled with

rFVIIa. Very few adverse events have been reported in these patients.^{27,37,39} In the vast majority of these cases, patients received doses at or around 90 $\mu\text{g}/\text{kg}$ but reported total doses ranged from 16 to 2280 $\mu\text{g}/\text{kg}$.^{23,37}

In some published reports,^{37,40,41} rFVIIa was effective at low doses in obstetric bleeding but in the ANZHR, the majority of patients received a single 90 $\mu\text{g}/\text{kg}$ dose, which is the recommended dose for patients with hemophilia. Further study is required before definitive recommendations regarding dosing in obstetric hemorrhage can be made.

Although no association was seen in our results between fibrinogen or platelet counts and the response to rFVIIa, it is likely that these laboratory results did not reflect the true physiological condition at the time of drug administration. Because it is a registry rather than a clinical trial, we are unable to mandate when laboratory tests are assessed in relation to the administration of rFVIIa. In a rapidly evolving environment such as obstetric hemorrhage, physiological conditions change within minutes, and it is probable that tests taken >30 min before the administration of the dose do not accurately reflect the patient's condition in this respect.

Recombinant FVIIa is a procoagulant protein, and its use therefore raises concerns about the potential for thrombotic complications. O'Connell et al.⁴² reported on thrombotic complications reported to the United States Food and Drug Administration adverse event reporting system. Although 185 thromboembolic adverse events were described, it is not possible to ascertain from their data whether this rate of events is different from that seen in our population of patients. In addition, the Food and Drug Administration adverse event reporting system is a voluntary system, and it is unlikely to have full capture of adverse events. Phase 2 and 3 placebo-controlled trials of rFVIIa in intracerebral hemorrhage,⁴³ liver surgery,^{44,45} pelvic reconstruction surgery,⁴⁶ and trauma²⁹ have not reported a higher incidence of thromboembolic complications in patients who received rFVIIa, although these trials may not have been adequately powered to assess this complication. It should also be noted, however, that randomized, controlled trials are likely to underestimate true rates of thromboembolism because patients at greatest risk of thromboembolism are typically excluded from these trials.

Six thromboembolic complications (1 splenic thrombosis, 3 pulmonary embolisms, 1 bilateral ovarian vein thrombosis, and 1 thrombus of jugular and subclavian veins) have been reported in obstetric patients receiving treatment with rFVIIa.^{27,37,39} The ANZHR data reported 2 definite and 1 potential thromboembolic event in 105 women who received rFVIIa for severe PPH. Given the time course of presentation of the pulmonary embolism and DVT events, it is not possible to exclude causal associations, and these complications are possibly related to treatment with rFVIIa.

It must be borne in mind that pregnancy and the postpartum period carry an increased risk of venous thromboembolism that is further increased as a result of emergency cesarean delivery, especially if followed by hysterectomy. A causal association is less clear in the patient with hypoxic-ischemic encephalopathy as the magnetic resonance imaging changes reported are comparable with those described in patients with severe anoxic insults.³⁴ The known increased risk of thrombosis in the peripartum patient population calls for careful consideration of the risks and benefits of rFVIIa in obstetric hemorrhage. Given the combination of thromboembolic risk factors, once bleeding is controlled, we recommend that practitioners consider the administration of low-molecular-weight heparin as thromboprophylaxis for all women who receive rFVIIa for an obstetric indication.

Given the direct and indirect financial cost of blood products, problems with access to specialty care and/or sufficient blood component therapy in some areas, and concern about complications of massive transfusion in terms of increased morbidity and mortality and length of stay, the possibility to reduce transfusion with use of rFVIIa is of interest to both clinicians and hospital administrators. However, no differences in operative blood loss or transfusion requirements have been demonstrated in the placebo-controlled clinical trials of rFVIIa in liver resection⁴⁵ and liver transplantation^{44,47} or pelvic reconstruction surgery,⁴⁶ although modest reductions were demonstrated in cases of blunt trauma.²⁹

rFVIIa is an expensive drug, with an average-sized single dose of 90 $\mu\text{g}/\text{kg}$ in a 70-kg patient estimated to cost approximately \$6500–7500 (€3900–4500). In consideration of the potential utility of such a medication, the economic and, in particular, personal costs (loss of fertility) of peripartum hysterectomy should not be underestimated. Knight³⁵ noted that 84% of women undergoing hysterectomy required ICU care, 20% required further surgery, 21% had damage to other organs, and 17% recorded other severe morbidities. If the use of rFVIIa is able to reduce the number of hysterectomies and avoid, or ameliorate, the associated morbidities, the high cost of the drug may be considered worthwhile. Randomized trials are required to investigate the potential efficacy of rFVIIa in reducing the need for peripartum hysterectomy.

Controlled, prospective studies are required before definitive answers can be given to the questions of efficacy and safety of rFVIIa. It remains true, however, that the drug is being used in our region, and it is important that information about its use, particularly in terms of adverse events, is reported in the absence of clinical trials.

Given what is known about its mechanism of action and the mechanism of normal clotting, it is not likely that rFVIIa will be maximally effective if it is administered when the platelet count and fibrinogen level

are low.^{17,18} Consequently, replacement of fibrinogen and platelets should remain the mainstay of treatment for PPH and, when possible, treatment of low levels should precede any treatment with rFVIIa.

Although desirable, recommendations of blood products administration in ratios up to and more than 1:1 (FFP/PRBCs) may not be possible to achieve in many hospitals in Australia and New Zealand. Although immediate access to resuscitation fluids, blood component therapy, and medical or surgical treatment is not usually an issue for tertiary care hospitals, in rural, regional, or outer metropolitan community hospitals access can be problematic. Only one-third of obstetric patients in the Registry were treated in tertiary referral hospitals. Even in well-resourced, major metropolitan hospitals, unexpected major PPH can challenge hospital resources. In Australia, FFP cannot currently be kept in a thawed state, resulting in at least a 20-min delay before any is available for transfusion. Our Registry data indicate that many patients were unlikely to have received FFP and PRBCs in the desired proportions, particularly if they received >10 U of PRBCs. In rural or regional hospitals servicing the vast majority of our region, with no blood bank on-site, blood products may be limited or nonexistent. Lack of equipment and/or experienced personnel limits options for surgical and radiological interventions. Particularly in these centers, rFVIIa may offer an important therapeutic option. Even in tertiary care centers, rFVIIa may provide an additional tool for treatment of intractable severe PPH.

An important decision is to determine the optimal time to administer rFVIIa during the treatment pathway for PPH. This decision may vary depending on available resources in individual centers but should consider issues relating to the impact of major blood product transfusion itself, i.e., whether there is any benefit in limiting exposure to blood products in terms of the actual cost of blood products, the potential depletion of blood bank stores, and possible adverse effects related to massive transfusion *per se*. These considerations must be balanced with possible side effects of treatment, most specifically an increase in the risk of thromboembolism in this patient population.

Management of severe PPH requires effective multidisciplinary teamwork to coordinate immediate patient resuscitation and to identify and treat the cause of bleeding. Risk factors for PPH can be identified in the antenatal and intrapartum periods and in these situations, preparations for the possibility of PPH should be undertaken. At the current time, the mainstay of treatment of PPH remains treatment of the primary cause of hemorrhage, restoration of blood volume, correction of coagulopathy, and appropriate surgical or radiological interventions. Randomized trials to assess the role of rFVIIa in the treatment of PPH are indicated.

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