



# The use of recombinant activated factor VII in trauma patients: Experience from the Australian and New Zealand haemostasis registry

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## KEYWORDS

rFVIIa;  
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## Summary

**Background:** There is increasing use of rFVIIa (eptagog alpha, Novoseven) in injured patients with critical bleeding. The role of rFVIIa is not defined in this group of patients. Registries provide an opportunity to review the patients, reported response and adverse events for rFVIIa.

**Aim:** To determine the pattern of use, reported response and adverse events in patients receiving rFVIIa following injury using the Australian and New Zealand Haemostasis Registry (ANZHR).

**Methods:** The ANZHR (commenced May 2005) collects data from 53 hospitals on all patients receiving rFVIIa in those hospitals.

**Results:** Of 695 cases in the registry, 108 patients from 19 hospitals were submitted with a primary trauma diagnosis. Most (88) patients received one 90 µg/kg dose of rFVIIa. There was a significant reduction in the use of all blood products following rFVIIa ( $p < 0.001$ ) and rFVIIa was thought to have decreased or stopped bleeding in 59% of cases. There was wide variation in the timing of rFVIIa use. There were two

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adverse events that were considered possibly linked and a total of three thromboembolic events. Following multivariate analysis, pH provided the best model of response to rFVIIa. Patients with a pH < 7.05 were significantly less likely to respond (OR = 0.3, 95% CI = 0.0–0.3). Only two patients would fit the criteria for the present prospective study of rFVIIa in trauma patients.

*Conclusion:* The best approach to managing critical bleeding in trauma patients is not agreed. The role of rFVIIa will only be clarified if there is a standardised approach to fluid management and transfusion of blood products. The registry allows tracking of current practice, outcomes and adverse events and will complement present phase 2 and 3 trials.

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## Introduction

There has been considerable debate regarding the role of rFVIIa (eptacog alpha, NovoSeven<sup>®</sup>) in controlling critical bleeding in non-haemophiliac patients. A number of anecdotal reports have been published, reporting promising results in a variety of refractory bleeding situations. Phase 2 randomised controlled clinical trials have been conducted in the areas of intracerebral haemorrhage,<sup>7</sup> liver surgery,<sup>4,5</sup> pelvic reconstruction surgery<sup>9</sup> and trauma.<sup>2</sup> Results from some of these trials have been positive,<sup>2,7</sup> however most have been unable to demonstrate significant outcome benefits,<sup>2,4,5,9</sup> although equivalence in safety, particularly thromboembolic safety has generally been demonstrated. While a number of phase 3 studies are in progress, the role of rFVIIa for critical bleeding indications in non-haemophiliac patients, including trauma, is currently not clearly defined.

rFVIIa (eptacog alpha, NovoSeven<sup>®</sup>) is approved by the Australian Therapeutic Goods Administration and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) for the control of bleeding and surgery prophylaxis in patients with inhibitors to coagulation factors VIII and IX. As there is ongoing use of rFVIIa in non-haemophiliac patients, and in the absence of definitive clinical trial results, there is a need to characterise patients receiving rFVIIa and evaluate efficacy and safety in these patients. Detailed information such as cause of bleeding, dose of rFVIIa, blood products and laboratory test results as well as outcomes and adverse events are critical to understanding the role of rFVIIa in refractory bleeding and in helping physicians to identify appropriate patients, doses and timeframes for treatment. This study reports on indications, patient types and outcomes of 108 trauma patients included in the Haemostasis Registry from Australia and New Zealand.

## Methods

The Haemostasis Registry contains details of non-haemophiliac patients treated with rFVIIa at parti-

cipating hospitals throughout Australia and New Zealand. The Haemostasis Registry has been established by Monash University (Department of Epidemiology and Preventive Medicine) with financial support in the form of an unrestricted educational grant from Novo Nordisk Pharmaceuticals Pty Ltd.

## Patients

The Haemostasis Registry began receiving data in May 2005 but includes cases dating back to 2001. Fifty-three hospitals from all States and Territories of Australia and from New Zealand are currently contributing data to the Registry. Hospitals commit when signing up to the Registry, to provide data from all cases of rFVIIa use at their hospital. Eligible patients are identified by local investigators following treatment with rFVIIa usually through pharmacy or haematology records. The registry has obtained ethics approval from the Human Research Ethics Committees of all participating hospitals to collect de-identified information without patient consent. Patients were included in this study if the primary cause of bleeding was as a result of trauma.

## Data

For the eligible cases, the following data were obtained from the Haemostasis Registry; patient demographics (age, gender, country, state), injury event (injury severity score [ISS], mechanism of injury), blood test results before and after rFVIIa dose (prothrombin time [PT], international normalised ratio [INR], activated partial thromboplastin time [APTT], haemoglobin, haematocrit, fibrinogen, platelet count), blood products use in the 24 h before and after rFVIIa dose (red blood cells [RBC], fresh frozen plasma [FFP], platelets and cryoprecipitate), dose event (date, time and place of administration, dose volume, pH, temperature) and mortality. In addition, prescribing clinicians were asked to assess patient response by indicating whether bleeding had stopped, decreased or was unchanged following the use of rFVIIa. Clinicians

were also asked to report all adverse events, with specific emphasis on thromboembolic events, within 28 days of treatment with rFVIIa and to give an assessment of whether, in the opinion of the investigator, these events were or were not linked to the administration of rFVIIa.

## Statistical analysis

Coagulation parameters and blood products before and after rFVIIa dose were compared using Wilcoxon matched-pairs signed-ranks tests. To assess the relationship between measurements and the outcomes of interest (response and mortality), both univariate and multivariate analyses were performed. Continuous variables were categorised based on clinical parameters. Chi-square analysis was used to identify associations between categorical baseline variables and the outcomes. Multivariate analysis was used to identify significant independent predictors of each outcome. A backward stepwise binary logistic regression procedure based on a likelihood method was employed. Variables demonstrating a univariate association of  $p \leq 0.10$  were included in the model. For each model, odds ratio and 95% CI were provided.

**Table 1** Overview of trauma patients included in the haemostasis registry

	No. (%) of trauma patients
<i>n</i>	108 (100)
Mechanism	
Blunt	95 (88)
Penetrating	11 (10)
Burns	2 (2)
Mechanism	
Motor vehicle occupant	36 (33)
Other transport related circumstance	35 (33)
Falls	5 (5)
Firearm	3 (3)
Cutting, piercing object	6 (6)
Burns	2 (2)
Other cause	21 (18)
ISS	101 (94)
<16	13 (12)
16–25	32 (30)
26–35	16 (15)
36–45	16 (15)
46–55	10 (9)
56–65	4 (4)
66–75	10 (9)

## Results

As at September 2006 the Haemostasis Registry database had received 695 cases. Of these, 108 patients (15%) from 19 hospitals were submitted with the primary cause of bleeding as a result of trauma.

The median (range) age of patients was 38 (11–91) years with 26% of patients under the age of 25 years and 23% 55 years of age or older. The majority of patients were male (76%). Patients were treated in all Australian mainland states and in New Zealand with the largest number treated in New South Wales (44%).

The majority of trauma (71 cases, 66%) occurred as a result of motor vehicle related incidents (Table 1). Injury severity scores (ISS) were obtained for 101 of the 108 cases. The median (range, IQR) ISS was 29 (4–75, 20–44).

The 108 trauma patients received a total of 128 doses of rFVIIa. Four patients received three consecutive doses and 16 patients received two doses with the remaining patients receiving a single dose of rFVIIa. The median (IQR) dose was 7.2 (6–8.4) mg or 90 (78–105)  $\mu\text{g}/\text{kg}$ .

Details of blood products received before and after the initial dose of rFVIIa are shown in Table 2. Five patients (5%) received no units of RBC at all before receiving rFVIIa, including one patient who received no blood products at all for religious reasons. There was a significant reduction in units of blood products received following the initial dose of rFVIIa ( $p < 0.001$ ).

pH data was unavailable for 23 (21%) patients at the time of initial rFVIIa dose. Of the remaining 85 patients, 74 (87%) were acidotic (pH less than 7.35) at the time of the initial rFVIIa dose including 19 patients (22%) who were moderately acidotic (pH 7.2–7.05) and 21 (19%) who were severely acidotic (pH < 7.05). Of the severely acidotic patients, nineteen died, fifteen of them within 12 h of arriving at hospital. The remaining two patients were still in hospital at 28 days following rFVIIa administration. In the groups with normal, mild or moderate acidosis, most patients (91%, 79%, and 68%, respectively) were living at 28 days following administration of rFVIIa.

Temperature was not recorded for 23 (21%) patients at the time of initial rFVIIa dose. Of the remaining cases 32 (38%) had a temperature below 35 °C including two patients (2%) with a temperature below 32 °C. Twenty-six patients were both hypothermic and acidotic. Fifteen of these patients died as a result of their injuries, three remained as inpatients at 28 days following rFVIIa administration and eight were discharged.

Details of coagulation parameters before and after the initial dose of rFVIIa are provided in Table 3. Prothrombin time (PT) was prolonged

**Table 2** Blood product usage in the 24 h before and after administration of the initial dose of rFVIIa

Blood product	Time relative to initial rFVIIa dose	Units	Number of cases (%)	Median (IQR)	Range	Z-score ( <i>p</i> -value) <sup>a</sup>
RBC	Before	0	5 (5)	16 (8–23)	0–59	7.4 (<0.001)
		1–5	8 (7)			
		6–10	23 (21)			
		11–20	41 (38)			
		>20	31 (29)			
	After	0	38 (35)	3 (0–8)	0–40	
		1–5	38 (35)			
		6–10	20 (19)			
		11–20	9 (8)			
		>20	3 (3)			
FFP	Before	0	13 (12)	8 (4–12)	0–44	5.9 (<0.001)
		1–5	25 (23)			
		6–10	36 (33)			
		11–20	31 (29)			
		>20	3 (3)			
	After	0	53 (49)	1 (0–4)	0–30	
		1–5	34 (32)			
		6–10	9 (8)			
		11–20	10 (9)			
		>20	2 (2)			
Platelets	Before	0	28 (26)	3 (0–6)	0–80	4.4 (<0.001)
		1–5	53 (49)			
		6–10	15 (14)			
		11–20	10 (9)			
		>20	2 (2)			
	After	0	57 (53)	0 (0–3)	0–16	
		1–5	42 (39)			
		6–10	7 (7)			
		11–20	2 (2)			
		>20	0 (0)			
Cryoprecipitate	Before	0	40 (37)	5 (0–10)	0–36	4.9 (<0.001)
		1–5	17 (16)			
		6–10	28 (26)			
		11–20	18 (17)			
		>20	5 (5)			
	After	0	79 (73)	0 (0–1)	0–35	
		1–5	14 (13)			
		6–10	7 (7)			
		11–20	5 (5)			
		>20	3 (3)			
Total blood products	Before	0	4 (4)	34 (19–51)	0–156	7.1 (<0.001)
		1–10	13 (12)			
		11–20	12 (11)			
		21–30	17 (16)			
		31–40	25 (23)			
		41–50	9 (8)			
		>50	28 (26)			
	After	0	30 (28)	7 (0–17)	0–100	

Table 2 (Continued)

Blood product	Time relative to initial rFVIIa dose	Units	Number of cases (%)	Median (IQR)	Range	Z-score ( <i>p</i> -value) <sup>a</sup>
		1–10	39 (36)			
		11–20	15 (14)			
		21–30	14 (13)			
		31–40	3 (3)			
		41–50	2 (2)			
		>50	5 (5)			

<sup>a</sup> Z-scores and *p*-values relate to Wilcoxon matched-pairs signed-ranks tests of individual values before and after initial dose of rFVIIa.

(>15.5 s) in 59 of 79 patients (75%) before administration of rFVIIa. Similarly, INR was prolonged (>1.5) in 58 of 75 patients (87%) before administration of rFVIIa. Seventy-one of 91 patients (88%) had prolonged PT or INR (or both) before rFVIIa administration.

All coagulation parameters except Haematocrit exhibited statistically significant changes after the initial dose of rFVIIa compared with before administration of rFVIIa (Table 3).

Recombinant rFVIIa was considered to have decreased or stopped bleeding in 53 (59%) of cases where efficacy was reported (total 90 cases). In the 37 patients where the initial dose of rFVIIa was considered not to have had an effect on bleeding, only 8 (22%) survived to hospital discharge (Fig. 1). Observed mortality for all patients at 28 days was 45 of 108 (42%). Of the patients who survived to 28 days, 7 (7%) were still in hospital at that time.

Twenty-six patients (24%) reported a total of 32 adverse events within 28 days of receiving rFVIIa. There were no adverse events that were considered to be 'definitely' or 'probably' linked to the administration of rFVIIa. In two cases (2%) adverse events were considered possibly related to rFVIIa administration. A total of three patients (3%) experienced thromboembolic adverse events.

Nine patients (8%) suffered multiple organ failure, and six patients (5%) suffered acute respiratory distress syndrome, none of which were considered to be related to rFVIIa administration.

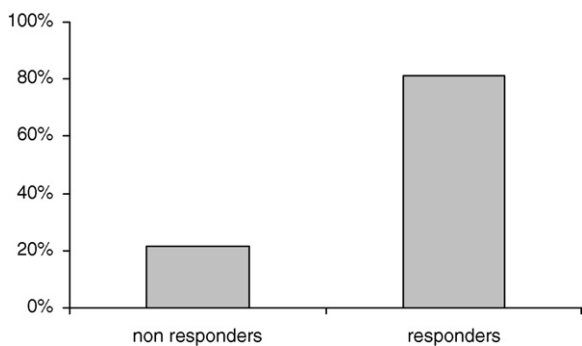
### Univariate analyses

Of the variables considered, gender, dose, temperature, haemoglobin level, platelet level, fibrinogen level, PT/INR, ISS and place of administration were not significantly associated with response. Factors that showed some association with response were

Table 3 Coagulation parameters before and after administration of the initial dose of rFVIIa

		Number of patients	Median (interquartile range)	Range	Z-score ( <i>p</i> -value) <sup>a</sup>
PT (s)	Before	79	20.0 (15.2–25.0)	10.2–104.0	5.4 (<0.001)
	After	78	13.1 (10.7–18.1)	8.6–100.0	
INR	Before	75	1.8 (1.4–2.3)	0.7–11.6	5.2 (<0.001)
	After	71	1.0 (0.9–1.5)	0.5–8.0	
APTT (s)	Before	91	54.5 (36.4–101.0)	26 to 300	2.9 (0.004)
	After	87	42.0 (35.0–66.0)	27 to 300	
Haemoglobin (g/L)	Before	100	85.0 (69.0–109.0)	8–147	2.2 (0.029)
	After	91	96.0 (79.0–113.0)	11–161	
Haematocrit (%)	Before	94	26 (21–33)	12–43	1.6 (0.107)
	After	87	28 (23–34)	14–80	
Fibrinogen (g/L)	Before	68	1.4 (0.9–1.8)	0.1–4.2	3.0 (0.003)
	After	63	1.7 (1.2–2.4)	0.4–4.7	
Platelet count ( $\times 10^9/L$ )	Before	99	85.0 (59.0–149.0)	13–310	2.4 (0.016)
	After	87	82.0 (52.0–109.0)	6–388	

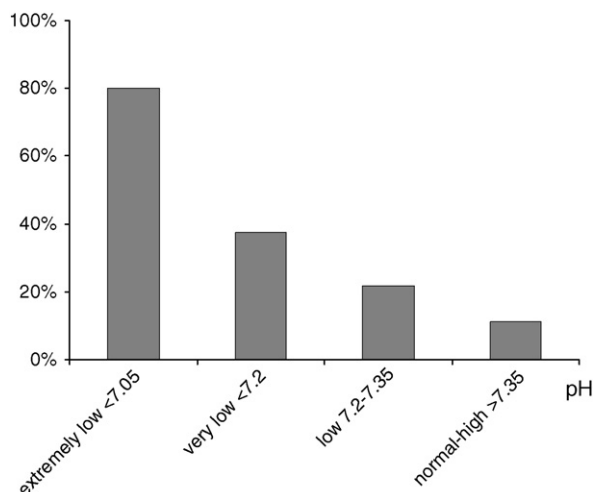
<sup>a</sup> Z-scores and *p*-values relate to Wilcoxon matched-pairs signed-ranks tests of individual values before and after initial dose of rFVIIa.



**Figure 1** Proportion of trauma patients alive at 28 days depending on the effect of rFVIIa on bleeding.

age ( $\chi^2_5 = 10.4, p = 0.065$ ), RBC units before dose ( $\chi^2_2 = 5.4, p = 0.068$ ), pH ( $\chi^2_3 = 21.7, p < 0.0001$ ) and time to dose ( $\chi^2_2 = 5.5, p = 0.062$ ). Patients receiving more units of RBC, with lower pH or with shorter time to dose were less likely to respond.

Mortality demonstrated an association with number of RBC units before dose ( $\chi^2_5 = 7.6, p = 0.054$ ), pH ( $\chi^2_3 = 32.9, p < 0.001$ ), temperature ( $\chi^2_1 = 5.2, p = 0.022$ ), ISS ( $\chi^2_1 = 11.4, p = 0.0012$ ), place of administration ( $\chi^2_2 = 4.8, p = 0.091$ ) and time to dose ( $\chi^2_2 = 8.0, p = 0.018$ ). Patients receiving more units of RBC, with lower pH, lower temperature, higher ISS, treated in ICU or with shorter time to dose were more likely to die.



**Figure 2** The proportion of trauma patients that respond to rFVIIa at different pH levels.

**Multivariate analyses**

Variables showing a significant univariate association were entered into the multivariate analyses, the results of which are provided in Table 4. The pH was found to provide the best model of prediction of patient response. Patients with pH less than 7.05 (OR = 0.3, 95% CI = 0.0–0.3) were significantly less likely to respond than patients with a normal pH (Fig. 2) (Table 5).

**Table 4** Details of possibly related adverse events and thromboembolic events within 28 days of administration of rFVIIa

Type of AE	Causality	Time after rFVIIa	Case details	Significant history	Outcome
PE	Possibly linked to rFVIIa	7 days	66yo male MVA, immobilised with pelvic #, suffers inferior AMI post injury, subsequent insertion of IABP, abdo compartment syndrome, sepsis day 4. PE on day 7 in RVC segmental branch.	HT and thyroid dysfunction	Deceased 14 days post rFVIIa from MOF following acute MI secondary to abdominal trauma, cardiomegally consistent with hypertensive heart disease.
DIC	Possibly linked to rFVIIa	<6 h	51yo female suffering blunt assault with complete avulsion of spleen and extensive liver lacerations.	Chronic liver disease, IDDM, pancreatitis and chronic alcohol abuse	Deceased from bleeding associated with injuries and DIC
PE	Unable to assess causality	23 days	38yo male MBA, multiple # including open book pelvic # and abdominal haematoma. At day 23 pt c/o shortness of breath and chest pain. CT revealed multiple bilateral PE.	Nil	Discharged
CVA	Not Linked	1–2 days	20yo female MVA, closed head injury, unstable pelvic #, R pneumothorax	Not known	Deceased 5 days post rFVIIa from injuries received

**Table 5** Multivariate analyses

Variable	Category	OR (95% CI)	p-Value
Response	pH >7.35 (ref)		0.003
	7.21–7.35	0.4 (0.0–3.6)	
	7.05–7.20	0.2 (0.0–2.4)	
	<7.05 <sup>a</sup>	0.0 (0.0–0.3)	
Mortality	pH >7.35 (ref)		0.013
	7.21–7.35	0.8 (0.1–11.9)	
	7.05–7.20	0.2 (0.0–5.8)	
	<7.05 <sup>b</sup>	53.6 (2.2–1324.4)	
	Temp ≥35.0 (ref)		
<35.0	5.6 (0.7–41.3)		
ISS	<26 (ref)		0.017
	≥26	10.1 (1.5–67.0) <sup>c</sup>	

<sup>a</sup> Patients with pH < 7.05 were significantly less likely to respond than patients with a normal pH.

<sup>b</sup> Patients with pH < 7.05 were significantly more likely to die than those with normal pH.

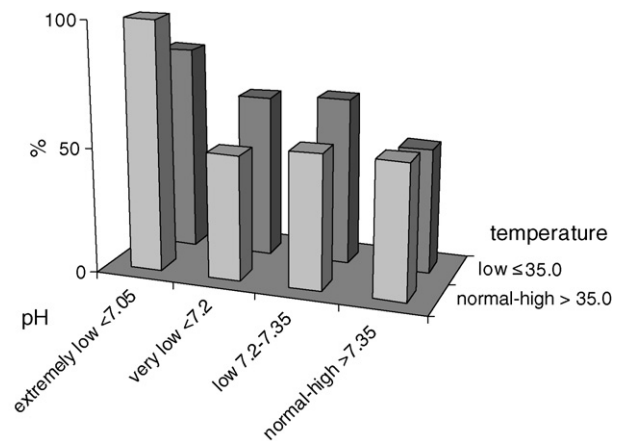
<sup>c</sup> Patients with ISS greater than or equal to 26 were significantly more likely to die than those with lower ISS.

Temperature, pH and ISS were found to contribute to the best model of prediction of mortality. Patients with a pH less than 7.05 were significantly more likely to die (OR = 53.6, 95% CI = 2.2–1324.4) than those with normal pH (Fig. 3) and patients with ISS of 26 or more were significantly more likely to die (OR = 10.1, 95% CI = 1.5–67.0) than patients with a lower ISS.

## Discussion

This is one of the largest series of trauma patients receiving rFVIIa outside a clinical trial. The treating clinicians documented that there was a therapeutic effect in more than half the patients. Very few patients appeared to have suffered major adverse events that could be linked to the administration of rFVIIa. In particular the number of major thromboembolic events appears to be low and comparable to that seen in other trauma populations.<sup>2</sup> Unlike a number of other reports<sup>8</sup> on adverse events, this series does not contain selectively reported cases but sequential cases from a number of hospitals. While we cannot guarantee that every case from each hospital is included, participating hospitals do undertake to supply all cases. Consequently this series is probably more representative of the pooled experience than a single centre case series or series from hospitals reporting only selective cases.

This series emphasises the importance of continued systematic collection of data on rFVIIa usage in



**Figure 3** The proportion of deaths in trauma patients by pH and temperature at time of rFVIIa administration.

trauma patients, despite the fact that there is an ongoing international trial of rFVIIa in trauma patients. The restrictive trial entry criteria will mean that patients in the trial do not reflect the likely spectrum of potential clinical indications in trauma patients once the trial has been completed (only 2% of registry patients meet the trial eligibility criteria). It is important that “off-label” use is tracked to ensure that adverse events are documented and reasons for use are evaluated. Although numbers in the registry are still small, over time it will be possible to match patients in this registry with the major trauma registries to track risk adjusted outcomes and adverse events.

There are wide variations in clinical treatment guidelines for massive transfusion in major trauma patients.<sup>6,10,11,13</sup> Marked geographic variations were evident in this series depending on local enthusiasm for different approaches. This study showed that a significant number of patients have received rFVIIa when there has been little or no blood transfused and similarly, in many cases, no attempt has been made to replace clotting factors or platelets. Of the 19 hospitals where rFVIIa was used for trauma cases, 15 indicated that rFVIIa should be used according to a massive transfusion protocol. In most cases this required 10 units of RBC to have been administered prior to rFVIIa (two hospitals required >6 units in 4 h or 10 units in 24 h). In four hospitals there was no reported protocol for the administration of rFVIIa although one of these hospitals is in the process of implementing a protocol. Despite this, one third of registry patients received rFVIIa before 10 units of RBC and another third had received more than 20 units of blood before receiving rFVIIa.

The high incidence of clotting and platelet disorders in this critically ill group of trauma patients may indicate a need for early use of clotting factors,

platelet replacement and/or rFVIIa (even prehospital). Many hospital protocols still require laboratory results to confirm clotting abnormalities before factor replacement. At present there is little evidence to guide the clinician with respect to presumptive management of clotting disorders early in the course of resuscitation. Certainly there is evidence that a significant group of trauma patients will arrive with bleeding abnormalities before any transfusion has occurred<sup>1,3,12</sup> whether early aggressive management with replacement of clotting factors and platelets alters outcome is not known.

Clearly there is a need to standardise the critical bleeding guidelines so that basic therapies (with some evidence base such as platelet transfusion) are instigated early in the resuscitation. An agreement on transfusion guidelines would also allow better comparison of outcomes rather than the present ad hoc system which permits multiple variations in practice, even in the same institution.

The precise dosing for trauma patients has been subject to discussion.<sup>2</sup> In this series, most patients received 90 µg/kg. There is a marked difference between this and the three doses (total of 400 µg/kg) used in the phase II and ongoing phase III trauma trials. Further study is required to identify appropriate dosage regimes.

Recombinant FVIIa appeared to be less effective with severe acidosis and or hypothermia. This is a critically ill group and although mortality is high, it is difficult to gauge the effect of rFVIIa. In this series, a number of patients with severe acidosis or hypothermia survived to leave hospital, after apparent success with rFVIIa therapy.

This study analysed data from a registry, consequently there are inherent limitations to the conclusions able to be drawn. Clinicians are unblinded as to the use of the drug and consequently some bias may occur in the reporting of the effect of rFVIIa. Only limited data is collected, thus full risk adjustment is not possible. Potential bias in selection of cases and reporting of adverse events has been limited by the undertaking of hospitals submitting data to the registry that they will endeavour to report all cases from their hospital. Although the cases submitted to date do not represent the full Australian and New Zealand experience of rFVIIa in trauma, it is anticipated that all major trauma centres will be contributing data to the registry in the near future.

In this case series there appeared to be a clinical effect of rFVIIa in 59% of patients. Poor response was associated with low pH and mortality with low pH, temperature and high ISS. The use of rFVIIa should only be considered as part of a massive transfusion protocol that includes administration of other blood

products (e.g., cryoprecipitate and platelets) and which addresses other reversible clinical parameters including pH and temperature. Monitoring use through a registry will allow comparisons of risk-adjusted outcomes between treating units and tracking of adverse events and will complement the findings from the phase II and ongoing phase III studies.

## Conflict of interest statement

All authors are members of the trauma special interest group of the Australian and New Zealand Haemostasis Registry and contributed to the design, interpretation and writing of this manuscript. The Australian and New Zealand Haemostasis Registry is supported by an unrestricted Educational grant from NovoNordisk Pharmaceuticals Pty Ltd. Dr. Michael Parr is a member of the steering committee for the 'Control' Study and member of an international trauma advisory group to Novo Nordisk. Dr. Gary Jankelowitz is an employee of NovoNordisk Pharmaceuticals Pty Ltd. None of the other authors or the steering group managing the Registry have a financial relationship with the company. There are no other potential financial conflicts of interest.

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