

This article was downloaded by:[Shamsilo, T. S.]
On: 15 September 2007
Access Details: [subscription number 782052010]
Publisher: Informa Healthcare
Informa Ltd Registered in England and Wales Registered Number: 1072954
Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Acta Obstetrica et Gynecologica Scandinavica

Publication details, including instructions for authors and subscription information:
<http://www.informaworld.com/smpp/title~content=t716100748>

Use of recombinant activated factor VII for massive postpartum hemorrhage

Nazli Hossain^a; Tahir Shamsi^b; Saeeda Haider^c; Nargis Soomro^d; Nusrat H. Khan^e; Ghuffrana Umer Memon^f; Tasneem Farzana^b; Saqib Ansari^b; Elizabeth W. Triche^g; Edward Kuczynski^h; Charles J. Lockwood^h; Michael J. Paidas^a

^a Yale Women and Children's Center for Blood Disorders, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

^b Bismillah Taque Institute of Health Sciences & Blood Disorders, Karachi, Pakistan

^c Surgical Intensive Care Unit, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan

^d Department of Obstetrics & Gynecology, Unit 2, Civil Hospital Karachi & Dow

University of Health Sciences, Karachi, Pakistan

^e Department of Obstetrics & Gynecology, Unit 3, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan

^f Department of Obstetrics & Gynecology, Unit 1, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan

^g Yale Center for Perinatal, Pediatric & Environmental Epidemiology, Yale University School of Medicine, New Haven, CT, USA

^h Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

Online Publication Date: 01 January 2007

To cite this Article: Hossain, Nazli, Shamsi, Tahir, Haider, Saeeda, Soomro, Nargis, Khan, Nusrat H., Memon, Ghuffrana Umer, Farzana, Tasneem, Ansari, Saqib, Triche, Elizabeth W., Kuczynski, Edward, Lockwood, Charles J. and Paidas, Michael J. (2007) 'Use of recombinant activated factor VII for massive postpartum hemorrhage', Acta Obstetrica et Gynecologica Scandinavica, 1 - 7

To link to this article: DOI: 10.1080/00016340701619324

URL: <http://dx.doi.org/10.1080/00016340701619324>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article maybe used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORIGINAL ARTICLE

Use of recombinant activated factor VII for massive postpartum hemorrhage

NAZLI HOSSAIN¹, TAHIR SHAMSI², SAEEDA HAIDER³, NARGIS SOOMRO⁴,
NUSRAT H. KHAN⁵, GHUFFRANA UMER MEMON⁶, TASNEEM FARZANA⁷,
SAQIB ANSARI⁷, ELIZABETH W. TRICHE⁸, EDWARD KUCZYNSKI⁹,
CHARLES J. LOCKWOOD⁹ & MICHAEL J. PAIDAS¹

¹Yale Women and Children's Center for Blood Disorders, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA, ²Bismillah Taque Institute of Health Sciences & Blood Disorders, Karachi, Pakistan, ³Surgical Intensive Care Unit, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan, ⁴Department of Obstetrics & Gynecology, Unit 2, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan, ⁵Department of Obstetrics & Gynecology, Unit 3, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan, ⁶Department of Obstetrics & Gynecology, Unit 1, Civil Hospital Karachi & Dow University of Health Sciences, Karachi, Pakistan, ⁷Bismillah Taque Institute of Health Sciences & Blood Disorders, Karachi, Pakistan, ⁸Yale Center for Perinatal, Pediatric & Environmental Epidemiology, Yale University School of Medicine, New Haven, CT, USA, and ⁹Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, CT, USA

Abstract

Objective. We hypothesised that patients with massive postpartum hemorrhage (PPH), defined as blood loss >1,500 ml, may benefit from the use of activated recombinant factor VII (rFVIIa). **Design.** Retrospective cohort study. **Setting.** Department of Obstetrics & Gynaecology, Dow University of Health Sciences. **Population.** Thirty-four women with a diagnosis of massive PPH. **Methods.** All patients with PPH who were admitted to the Department of Obstetrics & Gynecology and Surgical Intensive Care Unit of Civil Hospital Karachi, Pakistan, were included in the study. From March 2005 to October 2006, 34 patients fulfilled the criteria of massive PPH, of which 18 received rFVIIa to control bleeding, and 16 patients did not. Availability and cost of rFVIIa were the factors in drug allocation. **Main outcome measures.** Maternal mortality, correction of coagulopathy, the amount of blood products transfused and preservation of fertility. **Results.** Patients receiving rFVIIa had lower maternal mortality (5/18, 28% versus 8/16, 50%, OR: 0.04 (0.002, 0.83)), and received a lower number of packed red cell transfusions (4.0 ± 4.46 versus 9.61 ± 6.7 , p value 0.007), against the comparison group. Patients receiving rFVIIa had lower activated partial thromboplastin (median: 13.0; 25–75th percentile: –25.0, –8.0, signed rank $p < 0.0001$), and lower prothrombin times (median: –8.8; 25–75th percentile: –24.2, –4.8), after administration of drug. There was no significant difference in the rate of hysterectomy between the 2 groups (11/18 (61%) versus 6/16 (38%)). No adverse event attributable to rFVIIa was observed in the study. **Conclusion.** Activated recombinant factor VII can be a life-saving drug in patients with massive PPH.

Key words: Maternal mortality, massive postpartum hemorrhage, Pakistan, coagulopathy

Introduction

Massive postpartum hemorrhage (PPH) is defined as blood loss >1,500 ml, or a fall in haemoglobin concentration of 40 g/l, or transfusion of more than

10 units of blood (1). Massive PPH may be complicated by hypovolemic shock, disseminated intravascular coagulopathy, and acute respiratory distress syndrome due to massive transfusion (1).

The etiological factors for PPH include uterine atony, placental abnormalities, genital tract trauma and coagulation disorders, with uterine atony accounting for 80% of PPH cases (1). Increasing rates of Cesarean deliveries worldwide have also increased the incidence of placenta accreta and PPH (2).

Management of massive PPH requires transfusion of blood products in addition to medical and surgical manoeuvres. These include use of oxytocin, misoprostol and prostaglandins, frequently followed by surgical manoeuvres consisting of stepwise devascularisation of ovarian and uterine arteries, B-Lynch sutures, bilateral internal iliac ligation, arterial embolisation, and, finally, hysterectomy. These surgical methods are risky when performed in the setting of disseminated intravascular coagulation, resulting in overt bleeding from several sites. The need for surgical expertise in ligation of vessels, or transportation of severely ill patients to angiography suites in case of embolisation adds to maternal morbidity.

Activated recombinant factor VII (rFVIIa) has been developed for the treatment of bleeding episodes in haemophilia patients with inhibitors, and has also been found useful in patients with massive bleeding during surgery or in postpartum period (3,4). Administration of pharmacological doses of 90 µg/kg rFVIIa result in excessive thrombin generation (5). A tight haemostatic fibrin plug is subsequently formed. This fibrin structure has been found more resistant to fibrinolytic degradation, and, thus, helps to maintain haemostasis (6). There are a number of case reports on the use of rFVIIa in PPH (7–12). In this study, we describe our experience with 18 patients, the largest obstetrical experience with the use of rFVIIa for PPH at a single centre.

Patients and methods

In this retrospective cohort study, we evaluated the maternal outcome of all patients with massive PPH, at the Department of Obstetrics & Gynecology, Unit 2, Civil Hospital and Dow University of Health Sciences, Karachi, Pakistan. Civil Hospital, with 15,000 deliveries each year, serves a population of 14 million, and receives referrals from other city hospitals. We divided the cohort into 2 groups based upon the addition of rFVIIa to their care. During the study period, a total of 34 patients fulfilling the criteria of massive postpartum hemorrhage, as outlined above, were treated at our department. Information about demographic details, surgical procedure, blood and blood products transfused, dose and response to rFVIIa were obtained from their medical charts. Complete blood count and

coagulation profile were obtained every 12 h in both groups of patients. On discharge from intensive care, patients were followed during their hospitalisation and in the postpartum period. The women were treated according to standard protocol for the management of PPH, which includes medical and surgical measures, such as use of uterotonic agents, prostaglandins, internal iliac ligation and hysterectomy. These medical and surgical measures were applied in both groups of women. Activated recombinant factor VII was only administered in patients with massive PPH in whom medical and surgical methods failed to stop bleeding. Recombinant activated factor VII became available as a haemostatic agent for catastrophic hemorrhage in March 2005 at our institution. However, because of its limited availability and cost, some women with PPH received the drug while others did not. One consultant haematologist (T Shamsi) was responsible for rFVIIa administration, and obtaining informed consent from each family prior to drug administration. The protocol for administration of rFVIIa consisted of an initial dose of 70 µg/kg. A repeat dose given only in cases when bleeding continued ($n=3$). These patients were then compared with a control group ($n=16$), admitted during the same period in the Intensive Care Unit (ICU) of the hospital who fulfilled the criteria of massive PPH, but were managed by conventional methods only because of the limited availability of rFVIIa at our hospital. Main study outcomes were maternal mortality, correction of coagulation profile (prothrombin time, activated partial thromboplastin time) transfusion of blood products, preservation of fertility, and adverse drug events.

Statistical analysis

Data analyses were performed by co-investigators at Yale University (EWT, EK, CJL, and MJP) who were not directly involved in patient care, and were not blinded to the 2 allocation arms. Descriptive statistics included frequencies for categorical variables and medians, and 25–75th percentiles for continuous variables. Unadjusted associations between treatment group and baseline parameters were assessed using χ^2 tests for categorical variables and Kruskal–Wallis non-parametric tests for continuous variables. Among the patients treated with rFVIIa, pre-post changes in activated partial thromboplastin (aPTT) and prothrombin (PT) levels after administration of the drug were examined by calculating change scores for each variable, and testing their significance using the Wilcoxon signed rank test. Unadjusted and adjusted odds ratios (OR) and 95%

confidence intervals (CI) were calculated from logistic regression models. A final adjusted model was chosen using a backward elimination strategy. Potential confounders remained in the final model if they were independent risk factors for maternal mortality or if their removal resulted in a $\geq 10\%$ change in the treatment group parameter estimate. Potential confounders included cause of bleeding, type of delivery, gestational age at delivery, maternal age, baseline PT, baseline aPTT, and baseline haemoglobin.

Results

Patient characteristics and baseline haematological parameters are described in Table I. Over two-thirds of the women in both treatment groups were multiparous, with a median maternal age of approxi-

mately 29 years. The majority of women in both groups had term deliveries. Causes of bleeding in these women included medical or obstetric complications; namely, disseminated intravascular coagulation (DIC), systemic lupus erythematosus (SLE), hepatic failure, pregnancy induced hypertension with twin gestation, HELLP (Hemolysis Elevated liver enzymes, Low Platelet count), cervical tears or scar dehiscence; or, placental (i.e. placenta accreta, abruptio placentae, placenta previa) or uterine (i.e. uterine atony, ruptured uterus) etiologies. Over half of the women in both groups were delivered by Cesarean section. Women in the rFVIIa group had significantly lower haemoglobin levels than untreated women ($p=0.02$). Women treated with rFVIIa also had significantly higher PT and aPTT levels at baseline compared to untreated women ($p=0.03$ and $p=0.05$, respectively). No significant

Table I. Characteristics of the study population by treatment group.

	Women who received rVIIa* ($n=18$)		Women who did not receive rVIIa** ($n=16$)		p -value***
	N	%	n	%	
Cause of bleeding					0.83
Medical/ pregnancy disorder****	3	17.0	3	18.7	
Cervical/other†	3	17.0	1	6.3	
Placental††	6	33.0	6	37.5	
Uterine‡	6	33.0	6	37.5	
Type of delivery					0.57
LSCS	10	55.6	11	73.3	
NVD/other	8	44.4	4	26.7	
Surgical intervention					0.23
No surgery	3	16.7	8	50.0	
Surgery – uterus saved	2	11.1	1	6.2	
Surgical repair/subtotal	2	11.1	1	6.2	
Total hysterectomy	11	61.1	6	37.5	
Parity					0.90
Multiparous	12	66.7	11	68.8	
Primiparous	6	33.3	5	31.2	
Baseline haemoglobin (Hgb)					0.02
≥ 60 g/l	6	33.3	11	73.3	
< 60 g/l	12	66.7	4	26.7	
	Median	25–75th percentile	Median	25–75th percentile	p -value‡‡
Gestational age at delivery	40.0	(40.0–40.0)	40.0	(40.0–40.0)	0.05
Maternal age	29.0	(26.0–32.0)	28.5	(25.5–30.0)	0.56
Baseline PT	23.0	(17.2–39.0)	18.0	(14.0–21.0)	0.03
Baseline apt	50.0	(38.0–73.0)	38.0	(31.0–44.0)	0.05

*rFVIIa given when all conventional methods failed.

**Treated by conventional methods.

*** χ^2 p -value.

****Includes DIC, SLE, hepatic failure, PIH+twins, HELLP.

†Includes cervical tear, scar dehiscence.

††Includes placenta accreta, abruptio placenta, adherent placenta, placenta previa.

‡Includes uterine atony, ruptured uterus.

‡‡Kruskal-Wallis p -value.

Table II. Dosage and response to rFVIIa by treated patients*.

	<i>n</i>	%
No. doses		
Single dose	15	83.3
2 doses administered 3 h apart	3	16.7
Dose of rFVIIa (mg)		
3.6	8	44.4
4.8	10	55.6
Response to drug		
No response	2	11.1
Complete response after second dose	1	5.6
Complete response after first dose	15	83.3
Time to response**		
<20 minutes	6	37.5
≥20 to <30 minutes	7	43.7
≥30 minutes	3	18.7

*Includes 3 women who received 2 doses of drug (2.4 mg followed by 2.4 mg after 3 h).

**Includes only women who had some response to drug (*n* = 16).

differences in cause of bleeding, type of delivery, parity, or maternal age between the treatment groups were found.

Of the 18 women receiving the drug, 8 received a dose of 3.6 mg and 10 received 4.8 mg, including 3 women who received 2 doses of 2.4 mg 3 h apart (Table II). The majority of women (83.3%) had a complete response (less visible bleeding and improved coagulation profile) after administration of the first dose; only 2 women had no observed response to the drug even with repeated administration. Among the 16 women who had some response, 37% responded in <20 min, 44% between 20 and

30 min, and the remaining 19% took 30 min or longer to respond.

There was a significant decrease in aPTT after administration of drug (median: 13.0; 25–75th percentile: –25.0, –8.0, signed rank *p* < 0.0001). Similarly, reductions in PT were significant (median: –8.8; 25–75th percentile: –24.2, –4.8). All but 2 patients had decreases in their aPTT and PT values; 1 patient had an increase and 1 had no change in these parameters. Use of the drug was associated with a significant decrease in the number of blood transfusions. Compared to the study group, the comparison arm had significantly more blood transfusions (*p* value 0.007).

In the unadjusted analysis, 22% in the rFVIIa group died compared to 50% in the non-rFVIIa group (OR = 0.29, 95% CI: 0.06, 1.26; *p* = 0.09) (Table III). Mean baseline aPTT values (obtained upon diagnosis of massive PPH) approached statistical significance (*p* = 0.10), with higher aPTT values associated with increased likelihood of mortality. In the final adjusted model (Table IV), rFVIIa treatment significantly decreased the likelihood of death by 96% (OR = 0.04, 95% CI: 0.002, 0.83), after adjusting for baseline haemoglobin and aPTT. Higher aPTT levels were independently associated with an increased likelihood of death (OR = 1.06 per unit increase in aPTT, 95% CI: 1.00, 1.12).

Comments

In this study, we found rFVIIa to be a life-saving drug in patients with massive PPH. No adverse thromboembolic events were noted. There have

Table III. Unadjusted odds ratios and 95% confidence intervals for the association between rFVIIa treatment, patient characteristics, and maternal mortality.

	Total No.	Maternal mortality (%)	OR	95% CI
Treatment group				
No rFVIIa	16	50.0	Ref	
rFVIIa	18	22.2	0.29	(0.06, 1.26)
Delivery type				
NVD/other	12	41.7	Ref	
LSCS	21	28.6	0.56	(0.13, 2.48)
Cause of bleeding				
Other medical/pregnancy/cervical	10	50.0	Ref	
Placental	12	25.0	0.22	(0.03, 1.60)
Uterine	12	33.3	0.50	(0.09, 2.81)
Hemoglobin (at delivery) g/dl				
≥60 g/l	17	35.3	Ref	
<60 g/l	16	37.5	0.92	(0.21, 3.96)
aPTT (continuous) seconds	31	–	1.03	(0.99, 1.07)
PT (continuous) seconds	30	–	1.02	(0.99, 1.05)
Maternal age (in years)	34	–	1.00	(0.83, 1.20)
Gestational age at delivery (in weeks)	34	–	1.16	(0.78, 1.74)

Table IV. Final logistic regression model for the association between treatment group, patient characteristics, and maternal mortality.

	OR	95% CI
Treatment group		
No rFVIIa	Ref	
rFVIIa	0.04	(0.002, 0.83)
Haemoglobin (at delivery)		
≥ 60 g/l	Ref	
< 60 g/l	2.14	(0.15, 30.04)
aPTT (continuous)	1.06	(1.00, 1.12)

been numerous case reports and case series on the use of rFVIIa in postpartum hemorrhage, but we could find no other reports of more than 12 patients who used the drug at a single centre (12), and none had a comparison group.

According to the World Health Organization (WHO) estimates, 25% of all maternal deaths are due to hemorrhage in the postpartum period (13,14). The majority of these deaths are in developing countries, where 1 in 1,000 women die due to PPH. A number of medical agents have been introduced, along with the surgical manoeuvres to control hemorrhage. There are no large multi-centre, double-blind, randomised controlled trials to identify the best drug combinations, route, or dose of uterotonics for the treatment of primary PPH (15).

Activated recombinant factor VII is licensed for use in haemophiliacs with inhibitors, in patients with Glanzmann's thrombasthenia, factor VII deficiency, and in acquired haemophilia. Recently, there had been series of publications on the off label use of rFVIIa for postpartum hemorrhage (12,16). In a case series by Ahonen (12), rFVIIa was used along with concomitant arterial embolisation in 4 women with massive PPH. In these 4 women, bleeding was significantly reduced, but did not stop completely, after the use of rFVIIa. Sobieszczyk et al. reviewed 25 cases published in the literature for use of the drug in massive PPH, from 5 countries. In this series, patients were also receiving other anticoagulant therapy, such as heparin, coumarin, along with concomitant diseases including leiomyoma, cardiovascular diseases and renal diseases (6 patients). In these 25 cases, the drug was also used as a last resort, when all other methods to control bleeding had failed. Similarly, individual case reports have found the drug useful after massive hemorrhage following operative deliveries and after amniotic fluid embolism (7–9). As stated below, we do not have the facilities for arterial embolisation at our institute, and none of our patients were receiving any other

anticoagulant therapy. While these case series suggest that PPH cases may strongly benefit from rFVIIa therapy, none of these case series had a comparison group. Further, publication bias towards successful off-label use of new therapies would favour those for which the drug was found to have an effect.

Recombinant activated FVII (Novoseven, Novonordisk®) has been used for the control of bleeding in cardiac surgery, orthopaedic surgery, in surgical patients with massive bleeding, and in trauma patients (17), although it has not been found to effect the outcome in penetrating wounds (18). It acts by forming complexes with the exposed tissue factor (TF) in the absence of factor VII and factor X. Its activity occurs mainly at the site of injury, whereas systemic activity has been found to be low or absent even with the administration of large doses in patients without coagulopathy. There are currently no clinical tests to monitor the effectiveness of drug. We measured rFVIIa efficacy by comparing the number of units of packed red blood cells and other blood products transfused, change in PT, aPTT times, and visual assessment of rate of blood loss before and after the administration of drug.

A major strength of this study was the study design. We technically employed a historical cohort design to compare mortality outcomes in women meeting the definition of massive PPH who received the drug with those who did not receive the drug. Although subjects were not randomised to treatment group, a 'natural experiment' was created because the decision to administer the drug was based solely on availability of the drug at the time of the woman's hemorrhage (which was unrelated to patient or provider characteristics). Nonetheless, as the drug was administered (if available) only after other conventional methods failed, women in the rFVIIa group had worse baseline haematological parameters (Table I: haemoglobin, PT, aPTT) than those in the comparison group. These differences would tend to attenuate any effects, and this may, in part, explain the stronger effects for rFVIIa found in the adjusted logistic regression models (Table IV) than in the unadjusted analyses (Table III).

The incidence of PPH has been found to be high in primiparous women, and in women with low risk factors (19). In our study, two-thirds of the entire cohorts were multiparous. Possible reasons for the predominance of multiparity in our study patients may be poor nutritional status, anaemia and decreased elasticity in the uterine architecture, thus leading to uterine atony and PPH. In this study, placental abnormalities were the main reason for PPH. In the series by Ahonen, genital tract trauma

was the main etiological agent for massive PPH. Uterine atony has been considered a major cause of PPH, but the increasing rate of Cesarean section globally is making placental abnormalities a leading cause of PPH (2).

Hysterectomy, with consequent loss of fertility, is common sequelae in women with PPH. Apart from the psychosocial consequences, it is also associated with increased morbidity and mortality (20). In our data, hysterectomies were performed at least as often in the rFVIIa group as in the comparison group. However, this outcome was not assessed in this study because, particularly at the beginning of the study time period, the drug was administered as a last resort when all other treatment options (including hysterectomy) failed to control bleeding. As our confidence with the drug improved, we increasingly made the decision to administer the drug before hysterectomy, and our experience suggests that earlier drug administration may improve fertility outcomes, but this outcome will have to be examined more closely in future studies.

Our results support that timely administration of rFVIIa in women with massive PPH improves outcome. Protracted continuous bleeding, consumptive and dilutional coagulopathy, metabolic acidosis, hypothermia, all lead to a full blown DIC. Though there are no clear guidelines on the time of administration of rFVIIa, the consensus opinion is that it should be given before the onset of coagulopathy due to massive transfusion (21). Based on our experience, we recommend administering rFVIIa early in order to avoid dilutional coagulopathy.

There had been concern about the incidence of thrombosis with the use of rFVIIa. From 1996 to 2004, more than 700,000 standard doses (90–120 µg/kg) of rFVIIa were administered to several thousand haemophiliacs with inhibitors and to patients with other bleeding disorders (22). The incidence of serious adverse events, including myocardial infarction, stroke, pulmonary embolism and DIC was 1%. These patients, however, frequently had co-morbid factors, such as diabetes, atherosclerosis and hypertension. Though rFVIIa is considered quite safe, risks for thrombosis should be considered in all high risk situations that predispose to thrombosis and DIC. In our series of obstetric patients, there were no reports of adverse events, including myocardial infarction and thrombosis. There were also no adverse drug events noted in the Ahonen series, where the drug was used in a total of 12 patients at a single centre. Based on our data and other published literature, it appears that adverse events are very rare in previously healthy obstetric patients, even in the face of major hemor-

rhage. Future randomised trials that include larger numbers of women should examine these adverse outcomes more closely.

We had 5 deaths in our treatment group, and 8 in the comparison group. Our results are consistent with published literature, that patients with uncontrolled bleeding and persistent coagulopathy, despite transfusion of blood products and surgical intervention, have mortality rates of 40–60% (23). Among the 5 women in the treatment group who died, one was a multigravida patient with twin gestation and HELLP syndrome, who went into hepatic failure and died. The second death was due to multi-organ failure in a woman who received 100 units of blood and blood products in an effort to control bleeding, following obstetric hysterectomy. Though her bleeding decreased after 2 doses, she died 10 days later due to multiple organ failure. Activated recombinant FVII was given at a very late stage, when all other measures had been exhausted. Two other deaths were seen in women with placental abnormalities. The last death was seen in a patient who was transferred to the ICU in a state of hemorrhagic shock. Recombinant activated FVII was given, along with blood and blood products, but she developed renal failure after 10 days in ICU. Her bleeding did stop, but her renal changes became irreversible. Substandard surgical skills and suboptimal care in the ICU in the last 3 women were identified in a departmental audit as the major contributors to deaths. The 8 women (50%) who died in the comparison group (8/16) were due to multi-organ failure. We do not have facilities for uterine artery embolisation at our centre. Uterine artery embolisation has been found helpful in patients with uterine atony. Transportation of a moribund bleeding patient from delivery suite to radiology suite has raised concerns (11).

The mean time for the drug to respond in a particular situation is found to be between 16 and 20 min (11). Lack of response in this period in the absence of arterial bleeding may necessitate the use of a second dose. There remains considerable uncertainty about the minimum effective dosage. Most of the series have quoted a dose of 60–120 µg/kg for the achievement of haemostatic effect. Based on our data, we suggest a dose of 70 µg/kg for PPH, but more research on an appropriate dose is required.

The prohibitive cost of the drug is an issue which needs to be addressed. Haynes et al. compared the cost of the drug to the transfusion-related costs in massive hemorrhage in their series of patients, and found Novoseven more cost-effective (24). Ideally, cost should not be a constraint factor in life-saving

situations. Moreover, the high cost of the drug may be compensated by the eventual high cost of critical patient's care, with its associated morbidity and mortality. It is generally recommended that rFVIIa should not be given if a patient is considered medically irrevivable. In our study, the decision to give rFVIIa was based on drug availability.

The evidence from our study, together with the prior case reports on the use of rFVIIa for PPH, is encouraging. However, randomised controlled trials with larger numbers of patients are needed to define the role of rFVIIa in massive PPH.

Conclusion

In conclusion, our observations provide strong evidence for the use of rFVIIa in massive PPH that is unresponsive to conventional haemostatic measures. The available published data on the use of rFVIIa in obstetric hemorrhage has also been encouraging. The cumulative evidence points toward the need for a well-designed, randomised, controlled trial in obstetric patients, from which evidence-based guidelines can be developed.

References

- McLintock C. Postpartum haemorrhage. *Thromb Res.* 2005;(115 Suppl 1):65–8.
- Mazouni C, Gorincour G, Juhan V, Bretelle F. Placenta accreta: a review of current advances in prenatal diagnosis. *Placenta.* 2006 July;28(7):599–603.
- Hedner U. Recombinant factor VIIa (Novoseven) as a hemostatic agent. *Semin Hematol.* 2001;38(4 Suppl 12):43–7.
- Warren O, Mandal K, Hadjianastassiou V, Knowlton L, Panesar S, John K, et al. Recombinant activated factor VII in cardiac surgery: a systematic review. *Ann Thorac Surg.* 2007;83(2):707–14.
- Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood.* 2004;104(13):3858–64.
- Franchini M, Zaffanello M, Veneri D. Recombinant factor VIIa. An update on its clinical use. *Thromb Haemost.* 2005;93(6):1027–35.
- Bouwmeester FW, Jonkhoff AR, Verheijen RH, van Geijn HP. Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII. *Obstet Gynecol.* 2003;101(6):1174–6.
- Lim Y, Loo CC, Chia V, Fun W. Recombinant factor VIIa after amniotic fluid embolism and disseminated intravascular coagulopathy. *Int J Gynaecol Obstet.* 2004;87(2):178–9.
- Moscardo F, Perez F, de la Rubia J, Balerdi B, Lorenzo JI, Senent ML, et al. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol.* 2001;114(1):174–6.
- Shamsi TS, Hossain N, Soomro N, Hasan JA, Noorani M, Kazi S, et al. Use of recombinant factor VIIa for massive postpartum haemorrhage: case series and review of literature. *J Pak Med Assoc.* 2005;55(11):512–5.
- Segal S, Shemesh IY, Blumenthal R, Yoffe B, Laufer N, Ezra Y, et al. Treatment of obstetric hemorrhage with recombinant activated factor VII (rFVIIa). *Arch Gynecol Obstet.* 2003;268(4):266–7.
- Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening postpartum haemorrhage. *Br J Anaesth.* 2005;94(5):592–5.
- Ronsmans C. Maternal mortality: who, when, where, and why. *Lancet.* 2006;368(9542):1189–200.
- AbouZahr C, Wardlaw T, Stanton C, Hill K. Maternal mortality. *World Health Stat Q.* 1996;49(2):77–87.
- Mousa H, Alfirevic Z. Treatment for primary postpartum haemorrhage. *Cochrane Database Syst Rev.* (1):CD003249; 2007.
- Sobieszczyk S, Breborowicz GH, Platcanov V, Tanchev S, Kessler CM. Recombinant factor VIIa in the management of postpartum bleeds: an audit of clinical use. *Acta Obstet Gynecol Scand.* 2006;85(10):1239–47.
- Scarpellini S, Rizoli S. Recombinant factor VIIa and the surgical patient. *Curr Opin Crit Care.* 2006;12(4):351–6.
- Vincent JL, Rossaint R, Riou B, Ozier Y, Zideman D, Spahn DR. Recommendations on the use of recombinant activated factor VII as an adjunctive treatment for massive bleeding – a European perspective. *Crit Care.* 2006;10(4):R120.
- Mousa HA, Walkinshaw S. Major postpartum haemorrhage. *Curr Opin Obstet Gynecol.* 2001;13(6):595–603.
- Smith J, Mousa HA. Peripartum hysterectomy for primary postpartum haemorrhage: incidence and maternal morbidity. *J Obstet Gynaecol.* 2007;27(1):44–7.
- Karalapillai D, Popham P. Recombinant factor VIIa in massive postpartum haemorrhage. *Int J Obstet Anesth.* 2007;16(1):29–34.
- Abshire T, Kenet G. Recombinant factor VIIa: review of efficacy, dosing regimens and safety in patients with congenital and acquired factor VIII or IX inhibitors. *J Thromb Haemost.* 2004;2(6):899–909.
- Eikelboom JW, Bird R, Blythe D, Coyle L, Gan E, Harvey M, et al. Recombinant activated factor VII for the treatment of life-threatening haemorrhage. *Blood Coagul Fibrinolysis.* 2003;14(8):713–7.
- Haynes J, Laffan M, Plaat F. Use of recombinant activated factor VII in massive obstetric haemorrhage. *Int J Obstet Anesth.* 2007;16(1):40–9.