

# Use of recombinant activated factor VII in massive postpartum haemorrhage

Linda S. Bouma<sup>\*</sup>, Antoinette C. Bolte, Herman P. van Geijn

Free University Medical Centre, Department of Obstetrics and Gynaecology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands

Received 5 December 2006; received in revised form 31 May 2007; accepted 14 June 2007

## Abstract

**Objective:** Postpartum haemorrhage (PPH) remains an important cause of maternal morbidity and mortality. With regard to morbidity, preservation of the uterus is of paramount importance in fertile women. The objective of the study was to describe the cumulative experience of a cohort of women that were treated with recombinant factor VIIa.

**Study design:** In this retrospective, descriptive study we approached all departments of obstetrics and gynaecology in the Netherlands to find out if they had used rFVIIa for this indication. Twenty-seven cases were reported to us. To evaluate each case, we used a standardized case record form.

**Results:** The main cause of PPH was uterine atony (82%). In 21 cases rFVIIa was explicitly given to prevent a hysterectomy. This was successful in 16 cases (76%). Relevant reduction or complete cessation of bleeding after rFVIIa was noted in 24/27 cases (89%). There was a reduction in blood product requirements following rFVIIa administration. The dose of rFVIIa was variable and ranged from 16 to 128  $\mu\text{g}/\text{kg}$ .

**Conclusion:** There appears to be a role for the use of rFVIIa in PPH unresponsive to conventional therapy. Recombinant FVIIa can be helpful and avoid an emergency hysterectomy.

© 2007 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Postpartum hemorrhage; rFVIIa; Hysterectomy

## 1. Introduction

Despite therapeutic advances, severe postpartum haemorrhage (PPH) remains an important cause of maternal morbidity and mortality. In developed countries, 1–5% of all deliveries are complicated by PPH (blood loss of >1000 ml) [1]. Timely recognition and prompt intervention are crucial for successful management. The main cause of PPH is uterine atony.

The sequelae from massive blood loss – hypoperfusion, acidosis and hypothermia – lead to secondary coagulopathy and should be prevented or reversed as soon as possible. Conservative treatment of PPH comprises administration of uterotonics, vasopressin [2], tranexamic acid, treatment of hypovolemic shock by maintenance of adequate oxygenation, restoration of blood volume, and administration of

blood products, while simultaneously performing examination of the genital tract for lacerations and removal of retained placenta fragments [3]. If not successful surgical interventions may be necessary. Emergency hysterectomy may be life-saving but treatment that avoids hysterectomy is preferred [4–6].

A number of case reports have been published reporting successful use of recombinant activated factor VII (rFVIIa, NovoSeven<sup>®</sup>, Novo Nordisk, Denmark) for intractable PPH [7–14]. The haemostatic effect of rFVIIa is thought to be mediated by enhancing the rate of thrombin generation leading to a full thrombin burst providing a fully stabilized fibrin plug with a tight fibrin structure, making it resistant to premature lysis. Localized activity of rFVIIa on activated platelets explains its effect in patients with thrombocytopenia. This localized activity on the platelet surface and tissue factor suggests enhancement of haemostasis limited to the site of injury without systemic activation of the coagulation cascade [3,15].

<sup>\*</sup> Corresponding author. Tel.: +31 20 4444444.

E-mail address: [ls.bouma@vumc.nl](mailto:ls.bouma@vumc.nl) (L.S. Bouma).

However, individual case reports carry the risk of publication bias. To avoid such bias, we attempted a nationwide survey on cases with PPH in the Netherlands between 2000 and 2004 in which rFVIIa had been used. The study was performed to describe the cumulative experience of a cohort that was treated with rFVIIa during the postpartum period especially with regard to preventing hysterectomy.

## 2. Patients and methods

All departments of obstetrics and gynaecology in the Netherlands were approached by mail and asked if in their department rFVIIa had been used in obstetric cases between 2000 and July 2004. A total of 27 cases came to our knowledge. We verified completeness of the data by the manufacturer (NovoNordisk) as they are keeping account of issued packing.

In this descriptive study we used a standardized case record form to evaluate each case. We collected data on a number of variables (Table 1). All data were extracted from the original patient charts. The forms were completed by two of the authors (LSB and ACB).

Positive effect of rFVIIa administration was defined as (temporarily) reduction or cessation of bleeding as clearly stated in the patient chart. Preservation of the uterus was used as an end point of maternal morbidity.

DIC was diagnosed when at least three of the following coagulation parameters were present: platelet count  $< 100 \times 10^9 l^{-1}$ , increased prothrombin time (PT), increased activated partial thromboplastin time (aPTT), abnormal D-dimer, decreased fibrinogen, increased fibrinogen degeneration products (FDP).

## 3. Results

Data were collected on 27 patients. The relevant data for each patient are shown in Table 1. Table 2 shows the clinical characteristics of the 27 patients.

The causes of PPH are shown in Table 3. In the majority of cases (82%), uterine atony was the cause of bleeding and in 68% of the cases no other cause was present. The second most frequent cause of PPH was vaginal or cervical laceration (19%). Retained or suspected incomplete placenta was reported in 15% of deliveries (four cases), and there were three cases (11%) of placenta praevia. In two cases uterine rupture was at the basis of PPH.

In 23/27 (85 %) cases rFVIIa was administered before a hysterectomy was performed. In 21 of these cases rFVIIa was explicitly given in an attempt to prevent a hysterectomy and this aim was successfully achieved in 16 (76%) women. In the remaining five cases, hysterectomy was performed but with limited bleeding. In 3/27, rFVIIa administration did not result in a reduction of haemorrhage (Table 1).

Surgical intervention was necessary in 24 of 27 cases (Table 4). Hysterectomy following vaginal delivery was performed in 7/19 cases (37%). Hysterectomy after caesarean section was performed in 4/8 cases (50%). Laparotomy was performed twice for B-Lynch procedure prior to hysterectomy. Embolisation was performed in five cases prior to and in one case following rFVIIa administration. After rFVIIa, surgery other than a hysterectomy was performed in four patients (2× re-laparotomy, 1× B-Lynch procedure, and 1× embolisation).

Reduction or cessation of bleeding after rFVIIa was stated in 24/27 women (89%). A marked reduction in blood product requirements (FFP, red blood cells [RBC], and platelets) was noted following rFVIIa administration (Fig. 1). In 24 cases (89%), estimated blood loss prior to rFVIIa administration was more than 3 L and more than 8 RBC units were transfused. In 17 cases (63%), blood loss after administration of rFVIIa was less than 1 L (Table 1).

In all, 15/27 patients had a complete recovery without the need for hysterectomy and 9/27 recovered after hysterectomy. Three patients died.

At the time of rFVIIa administration, most coagulation parameters were pathologic and in 88% of cases DIC was present. Laboratory tests showed correction of PT and aPTT within 6 h of rFVIIa administration in 70% of cases, although in 89% of cases platelet counts remained pathologic for 24 h after rFVIIa infusion. Only 2 cases of DIC were recorded to persist 24 h after rFVIIa administration.

Recurrent bleeding episodes were recorded in three cases (11%) and a thromboembolic event (pulmonary embolism) was diagnosed in one case 10 days postpartum.

The mean rFVIIa dose per administration was  $79 \pm 25 \mu\text{g}/\text{kg}$  (3.9 KIU/kg) ranging from 16 to 128  $\mu\text{g}/\text{kg}$ .

In all cases medications were given prior to or concurrently with rFVIIa administration. These included: oxytocin (88%); prostaglandin E<sub>2</sub> (93%); tranexaminic acid (56%); prothrombin complex concentrate (26%); desmopressin (DDAVP) (11%); ergometrine (11%). The concomitant uterotonic drugs used most frequently in this case series were oxytocin and/or prostaglandin E<sub>2</sub>. In a few cases relatively high doses of prostaglandin E<sub>2</sub> were used and in six cases (cases 4, 11, 12, 16, 22, 27) one or more ampoules of 500  $\mu\text{g}$  were injected directly into the uterus.

## 4. Discussion

Originally rFVIIa for treatment of patients with haemophilic disorders [16]. At the time coagulopathy was considered a contraindication for its use. However, since 1999, rFVIIa has been reported in life-threatening bleeding in surgical, trauma and obstetric patients [17]. Published case reports have recorded successful use of rFVIIa in PPH. Publication bias is likely. Boehlen et al. [18] reviewed the literature up to 2004 about rFVIIa and PPH and found 14

Table 1  
Short list of collected data

	G	P	Main cause	Surgical intervention <sup>a</sup>	Blood loss before rFVIIa (L)	RBC (U)	Platelets (U)	FFP (U)	Total dose rFVIIa (KIU)	Blood loss after rFVIIa (L)	RBC (U)	Platelets (U)	FFP (U)	Failure of rFVIIa	Maternal death
Case 1	2	1	Placenta praevia/accreta	1, 2, 3	>3	12	0	4	180	>3	28	3	7	Yes	No
Case 2	2	1	Uterine atony	2, 3	>3	24	3	14	240	<1	4	0	4	No	No
Case 3	1	0	Uterine atony	1, 4	>3	11	0	4	360	<1	2	0	0	No	No
Case 4	10	6	Uterine atony	1, 3	>3	18	3	6	360	>3	13	1	4	No	Yes
Case 5	1	0	Uterine atony	3, 4	>3	39	2	32	720	<1	3	2	8	No	No
Case 6	3	1	Uterine atony	1	>3	13	2	8	180	<1	3	0	0	No	No
Case 7	1	0	Uterine atony	1, 2, 3, 5	>3	13	2	6	?	2–3	12	1	4	Yes	No
Case 8	6	2	Uterine atony	1, 6	>3	24	6	6	900	<1	5	2	0	No	No
Case 9	1	0	Uterine inversion	1, 9	>3	18	2	8	240	<1	2	0	0	No	No
Case 10	1	0	Uterine atony	1, 2, 3	>3	16	3	4	1 ampoule	>3	10	4	6	No	No
Case 11	2	1	Uterine atony	1	>3	7	1	3	480	<1	4	0	1	No	No
Case 12	2	1	Uterine atony	1, 7	>3	6	0	3	2 ampoules	<1	2	1	0	No	No
Case 13	4	2	Uterine rupture/AFE	3, 4, 8	>3	48	9	19	2 ampoules	>3	26	4	19	No	No
Case 14	2	1	Sepsis	1	2–3	7	1	3	300	<1 (pt died)	0	0	0	No	Yes
Case 15	1	0	Uterine atony	2, 3	>3	9	2	6	300	>3	13	3	13	Yes	No
Case 16	1	0	Uterine atony	3, 5, 8	>3	8	1	8	340	1–2	12	2	4	No	Yes
Case 17	1	0	Uterine atony	0	>3	7	2	4	480	<1	0	0	0	No	No
Case 18	2	1	Uterine atony	1	>3	6	0	3	315	1–2	4	1	2	No	No
Case 19	1	0	Uterine atony	1, 4, 5	>3	8	0	2	270	1–2	6	0	6	No	No
Case 20	1	0	Uterine atony	1, 2	>3	10	0	3	340	<1	4	0	0	No	No
Case 21	1	0	Uterine atony	0	2–3	7	0	5	?	<1	0	0	0	No	No
Case 22	1	0	Uterine atony	3, 4	>3	22	1	12	2 ampoules	<1	2	0	5	No	No
Case 23	1	0	Uterine atony	0 (Jehovah's witness)	2–3	0	0	0	1 ampoule	<1	0	0	0	No	No
Case 24	2	1	Uterine atony	1, 7	>3	8	2	8	180	<1	0	0	0	No	No
Case 25	2	1	Uterine rupture	3	>3	0	0	0	240	1–2	11	0	4	No	No
Case 26	1	0	Uterine atony	1	>3	5	2	0	?	<1	2	1	1	No	No
Case 27	1	0	Uterine atony	1, 7	>3	16	1	8	300	<1	3	2	2	No	No

<sup>a</sup> 1 = tamponade; 2 = embolisation; 3 = hysterectomy; 4 = ligation internal iliac arteries; 5 = B-lynch procedure; 6 = laparotomy; 7 = repair of lacerations; 8 = re-laparotomy; 9 = repositioning of the uterus; 0 = none; G = gravidity; P = parity; RBC = red cell units; Plts = platelets; FFP = fresh frozen plasma units; AFE = anaphylactic syndrome of pregnancy (amniotic fluid embolism).

Table 2  
Clinical characteristics of the 27 patients

Obstetric history	
Previous cesarean section	5 (18%)
Previous PPH	2 (7%)
Current pregnancy	
Maternal age (years)	34 ± 4.3
Weight (kg)	76 ± 19
Nulliparous	15 (55%)
Twins	6 (22%)
Gestational age at delivery (wks)	39.2 ± 2.0
Augmentation of labor	8 (30%)
Caesarean section	8 (30%)
Operative delivery	10 (37%)
Spontaneous delivery	9 (33%)

Table 3  
Causes of PPH

	Number of patients (%)
Uterine atony	22 (82)
Genital tract lacerations	5 (19)
Retained placental fragments	4 (15)
Placenta praevia	3 (11)
Placenta accreta/percreta	2 (7)
Uterine rupture	2 (7)
DIC other than secondary to PPH	2 (7)

cases of which 13 were rated successful. In 4/14 cases the uterus was preserved. We tried to collect all cases of PPH treated with rFVIIa between 2000 and July 2004. In our case series of 27 patients use of rFVIIa was successful in 24.

In 21 cases rFVIIa was given explicitly to avoid hysterectomy. This was achieved in 16 cases (76%) according to the obstetrician in charge. There was a reduction in requirement for blood products after rFVIIa administration (Fig. 1). Administration of rFVIIa occurred mostly after more than 3 L of blood loss. In two surviving of three patients that received rFVIIa after less than 3 L of estimated blood loss, no other therapy was necessary. One of these patients was a Jehovah's Witness.

In our series there were three maternal deaths. The cause of death in the first patient (case 4) was serious brain damage after cardio-pulmonary resuscitation (CPR)

Table 4  
Surgical interventions

	Number of patients (%)
Surgery (all)	24 (89)
Manual checking for placental fragments	19 (70)
Uterine packing	16 (60)
Emergency hysterectomy (total)	11 (41)
Hysterectomy before rFVIIa	4 (15)
Hysterectomy after rFVIIa	9 (33)
Laparotomy after vaginal delivery	9 (33)
Embolicisation	6 (1 × after rFVIIa) (22)
Ligation iliac arteries	6 (22)
Re-laparotomy	5 (2 × after rFVIIa) (19)
B-lynch procedure	3 (1 × after rFVIIa) (11)

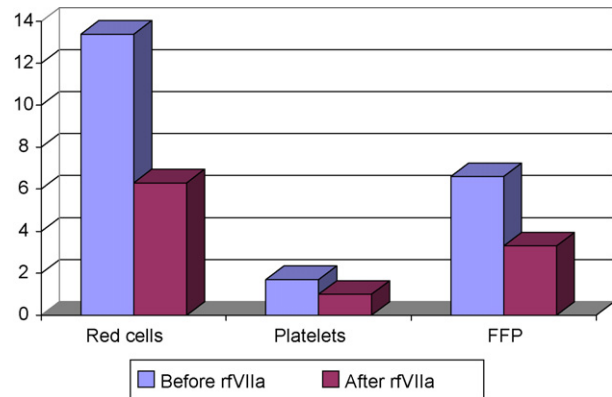


Fig. 1. Number of administered blood products before and after rFVIIa.

twice over an extended time period. She died 18 days later. In the second patient (case 14) the cause of death was irreversible shock with multiple organ failure due to an at that time not recognized group A streptococci sepsis (confirmed by cultures post mortem). This is the patient with less than 3 L blood loss in whom rFVIIa was not successful (Table 1). Recombinant FVIIa was administered during operative removal of the placenta 20 min before her death to treat uterine bleeding. The last patient (case 16) had circulatory collapse with cardiac arrest and was successfully resuscitated. A B-lynch procedure was performed. This was insufficient and an emergency hysterectomy was done. A few hours later a relaparotomy was considered necessary and rFVIIa was administered preoperatively. Shortly after the decision to undertake relaparotomy the EKG showed a dying heart pattern and she died.

Most patients received medications concurrent to rFVIIa and some, especially prostaglandin E2, may have caused adverse events. Although massive blood loss can precipitate cardiac problems, prostaglandin E2, a synthetic prostaglandin with potent uterotonic action, has been associated with cardiac complications when used during obstetric procedures [19–21].

Cardiac arrest occurred in four patients (4, 5, 16, 27). Three of these arrests occurred after intramyometrial administration of 500 (1 ×) to 1000 (2 ×) µg prostaglandin E2. Because of the course of events a relation with prostaglandin E2 was suspected. rFVIIa had not been administered yet.

Randomized trials with rFVIIa are scarce [22–24]. Some trials show a small increase in thrombo-embolic events after rFVIIa administration [25–26]. A comparison between these and our patients appears inadequate, as the patients were older and with co-morbidity. One venous thrombo-embolic event occurred in our series (pulmonary embolism 10 days postpartum). There were no arterial thrombotic events. The dosage of rFVIIa used varied greatly, probably reflecting the limited experience with its use. The recommended start dose is 90 µg/kg (4.5 KIU/kg). In our series, the mean rFVIIa dose given was 79 µg/kg per administration.

Our data indicate that there can be a role for rFVIIa in the management of massive PPH. rFVIIa might prevent hysterectomy and appears to reduce bleeding. Ideally, a randomized controlled trial is needed to clarify whether rFVIIa is really this effective, although the difficulties of randomization in this setting are recognized.

We want to make clear that it is not our intention to promote the off-label use of an expensive treatment.

Postpartum haemorrhage is a description of an event and not a diagnosis. A management protocol for treatment of massive obstetric hemorrhage should be available at every delivery unit. This protocol is directed at prevention of the severe maternal complications of massive PPH: hypovolemic shock disseminated intravascular coagulation, renal failure, hepatic failure and adult respiratory distress syndrome. Acute management of PPH involves restoration of blood volume and establishing the cause of bleeding. Several therapies have been used to control the bleeding: medical therapies include oxytocin, ergot alkaloids, prostaglandins, tranexamic acid, vasopressin and recombinant activated factor VII; surgical procedures include suturing, uterine packing, uterine artery or internal iliac artery ligation; and interventional radiology. When medical therapies and conservative surgical procedures fail to control the bleeding, hysterectomy is usually needed as a final measure to control the bleeding. However, peripartum hysterectomy is a radical procedure that has the undesirable side effects of infertility and physical and psychological trauma. In cases of intractable bleeding before converting to hysterectomy a promising non-invasive measure is administration of recombinant activated factor VII, of which haemostatic action is supposed to be limited to the bleeding site without systemic activation of coagulation. A combination of medical and surgical methods is possible [27].

The major limitation of this study is that the data have been collected retrospectively. We realize that thereby the favourable results can be biased. A comparison with adequate controls is very difficult due to the way in which deliveries and their complications are registered in most hospitals. Multiple interventions occurred in these patients and attribution of benefit to any of them is difficult. This surely limits the interpretation of the data.

## 5. Conclusion

Although a number of simultaneous interventions are undertaken in patients with massive PPH, there appears to be a role for rFVIIa in PPH unresponsive to conventional therapy. Decreased bleeding rates and avoidance of hysterectomy in a considerable number of patients included in the study suggest benefit. Further controlled investigations are required. In the rare situation of unresponsive haemorrhage where emergency hysterectomy appears to be the only resolution we think administration of rFVIIa should be considered.

## Condensation

Analysis of 27 cases using rFVIIa in the management of massive postpartum hemorrhage shows potential in decreasing blood loss and preventing hysterectomy.

## Acknowledgments

No financial support was received.

## References

- [1] The prevention and management of postpartum hemorrhage, WHO report of technical working group, Geneva: World Health Organization; 1990. Report No. WHO/MCH/90.7.
- [2] Lurie S, Mamet Y. Transient myocardial ischemia may occur following subendometrial vasopressin infiltration. *Eur J Obstet Gynecol Reprod Biol* 2000;91:87–9.
- [3] Bonnar J. Massive obstetric hemorrhage. *Ballieres Best Pract Res Clin Obstet Gynaecol* 2000;14:1–18.
- [4] Castaneda S, Karrison T, Cibils LA. Peripartum hysterectomy. *J Perinat Med* 2000;28:472–81.
- [5] Engelsen IB, Albrechtsen S, Iversen OE. Peripartum hysterectomy-incidence and maternal morbidity. *Acta Obstet Gynecol Scand* 2001;80:409–12.
- [6] Zelop CM, Harlow BL, Frigoletto FD, Safon LE, Saltzman DH. Emergency peripartum hysterectomy. *Am J Obstet Gynecol* 1993;168:1443–8.
- [7] Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. *J Trauma* 2001;51:431–8.
- [8] Breborowitz GH, Sobieszcyk S, SzykmanKIUwicz M. Efficacy of recombinant activated factor VII (rFVIIa, NovoSeven) in prenatal medicine. *Arch Perinat Med* 2002;8:21–7.
- [9] Zupancic SS, Sokolic V, Viskovic T, Sanjug J, Simic M, Kastelan M. Successful use of recombinant factor VIIa for massive bleeding after caesarean section due to HELLP syndrome. *Acta Haematol* 2002;108:162–3.
- [10] Bouwmeester FW, Jonkhoff AR, Verheijen RHM, van Geijn HP. Successful treatment of life-threatening postpartum hemorrhage with recombinant activated factor VII. *Obstet Gynecol* 2003;101:1174–6.
- [11] Sobieszcyk S, Breborowicz GH, Markwitz W, Mallinger S, Adamski D, Kruszynski Z. Effect of recombinant factor VII (RFVIIA; NovoSeven) in a patient in haemorrhagic shock after obstetrical hysterectomy. *Ginekol Pol* 2002;73:230–3.
- [12] Moscardo F, Perez F, dela Rubia J, Balerdi B, Lorenzo JI, Senent ML, Aznar I, Carceller S, Sanz MA. Successful treatment of severe intra-abdominal bleeding associated with disseminated intravascular coagulation using recombinant activated factor VII. *Br J Haematol* 2001;114:174–6.
- [13] Ahonen J, Jokela R. Recombinant factor VIIa for life-threatening postpartum haemorrhage. *Br J Anaesth* 2004;94:592–5.
- [14] Tanchev S, Platikanov V, Karadimov D. Administration of recombinant factor VIIa for the management of massive bleeding due to uterine atonia in the post-placental period. *Acta Obstet Gynecol Scand* 2005;84:402–3.
- [15] Hoffman M, Monroe III DM, Roberts HR. Activated factor VII activates factors IX and X on the surface of activated platelets: thoughts on the mechanism of action of high-dose activated factor VII. *Blood Coagul Fibrinolysis* 1998;9:S61–5.

- [16] Pehlivanov B, Milchev N, Kroumov G. Factor VII deficiency and its treatment in delivery with recombinant factor VII. *Eur J Obstet Gynecol Reprod Biol* 2004;116:237–8.
- [17] Mayo A, Misgav M, Kluger Y, Geenberg R, Pauzner D, Klausner J, et al. Recombinant activated factor VII (Novoseven<sup>TM</sup>): addition to replacement therapy in acute, uncontrolled and life-threatening bleeding. *Vox Sanguinis* 2004;87:34–40.
- [18] Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, de Moerloose P. Prolonged treatment of massive postpartum hemorrhage with recombinant factor VIIa: case report and review of the literature. *Br J Obstet Gynaecol* 2004;111:284–7.
- [19] Chen FG, Koh KF, Chong YS. Cardiac arrest associated with PGE2e use during caesarean section. *Anaesth Intensive Care* 1998;26:298–301.
- [20] Beerendonk CC, Massuger LF, Lucassen AM, Lerou JG, van den Berg PP. Circulatory arrest following PGE2e administration in postpartum hemorrhage. *Ned Tijdschr Geneesk* 1998;142:195–7.
- [21] Krumnickl JJ, Böttiger BW, Strittmatter HJ, Motsch J. Complete recovery after 2 h of cardiopulmonary resuscitation following high-dose prostaglandin treatment for atonic uterine hemorrhage. *Acta Anaesthesiol Scand* 2002;46:1168–70.
- [22] Friederich PW, Henny CP, Messelink EJ, Geerdink MG, Keller T, Kurth KH, Buller HR, Levi M. Effect of recombinant activated factor VII on perioperative blood loss in patients undergoing retropubic prostatectomy: a double-blind placebo-controlled randomised trial. *Lancet* 2003;361:201–5.
- [23] Lodge JP, Jonas S, Oussoultzoglou E, Malago M, Jayr C, Cherqui D, et al. Recombinant coagulation factor VIIa in major liver resection: a randomized, placebo-controlled, double-blind clinical trial. *Anesthesiology* 2005;102:269–75.
- [24] Raobaikady R, Redman J, Ball JAS, Maloney G, Grounds RM. Use of activated recombinant coagulation factor VII in patients undergoing reconstruction surgery for traumatic fracture of pelvis or pelvis and acetabulum: a double blind, randomized, placebo-controlled trial. *Br J Anaesth* 2005;94:586–91.
- [25] Mayer SA, Brun NC, Bergtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant activated factor VII intracerebral hemorrhage trial investigators, recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2005;352:777–85.
- [26] Jeffers L, Chalasani N, Balart L, Pysopoulos N, Erhardtsen E. Safety and efficacy of recombinant factor VIIa in patients with liver disease undergoing laparoscopic liver biopsy. *Gastroenterology* 2002;23:18–126.
- [27] Bouwmeester FW, Bolte AC, Van Geijn HP. Pharmacological and surgical therapy for primary post partum hemorrhage. *Curr Pharm Des* 2005;11:759–63.