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Recombinant human factor VIIa prevents hysterectomy in severe postpartum hemorrhage: single center study

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Abstract

Objective: To evaluate the effectiveness of human recombinant activated factor VII (rhFVIIa, NovoSeven) in avoiding hysterectomy postpartum in the management of severe postpartum hemorrhage (PPH).
Methods: We performed a prospective cohort study at our university tertiary care center. Patients with severe post partum hemorrhage (blood loss >2000 mL) and failed medical and uterus-preserving surgical management, were treated with intravenous bolus administration of rhVIIa. Main outcome measures were cessation of bleeding, postpartum hysterectomy and thromboembolic events.
Results: In 20/22 patients included, PPH was caused primarily by uterine atony, including 7 (32%) with additional lower genital tract lesion; in two women, it was due to pathologic placentation (placenta increta, 9%). One case of amniotic fluid embolism and one woman with uterine inversion were included. Recombinant hFVIIa was successful in stopping the PPH and in preventing a hysterectomy in 20/22 women (91%). The remaining two patients with persistent bleeding despite rhFVIIa treatment, who underwent postpartum hysterectomy, had placenta increta. No thromboembolic event was noticed.
Conclusions: This study describes the largest single center series of rhFVIIa treatment for fertility preservation in severe postpartum hemorrhage published to date. Our data suggest that administration of rhFVIIa is effective in avoiding postpartum hysterectomy after conservative medical and surgical measures have failed. Although randomized studies are lacking, rhFVIIa should be considered as a second-line therapeutic option of life-threatening postpartal bleeding, in particular if preservation of fertility is warranted and hysterectomy is to be avoided.

Keywords: Hysterectomy; postpartum hemorrhage; rhFVIIa.

Introduction

Major hemorrhage in the early postpartum period [postpartum hemorrhage (PPH)] represents one of the most common causes for maternal mortality and morbidity worldwide [18]. Life-threatening postpartal bleeding remains a challenging operative and/or medical treatment and may be caused by an incomplete expulsion of the placenta, by morbid placental adhesion, such as increte or percrete placentation, by uterine atonia, lower genital tract lacerations, uterine rupture or uterine inversion or by primary or secondary coagulopathy [6].

Medical treatment usually includes uterotonic agents, such as intravenous oxytocin, methylergometrine, misoprostol or prostaglandin E2 (sulprostone) [28]. Surgical interventions include the removal of the placenta or its remaining pieces, transvaginal surgical revision of genital lacerations, uterine tamponade (e.g., by balloon catheter), uterine packing, laparotomy, uterine compression sutures, such as brace sutures (e.g., Hayman technique [10], B-Lynch sutures or square sutures), stepwise uterine devascularization or hypogastric artery ligation [13]. Embolization of both uterine arteries is another option to treat severe postpartum hemorrhage; however, logistic prerequisites with 24-h availability of emergency interventional radiology are necessary. If conservative medical and surgical measures fail, emergency hysterectomy is often the last possibility to stop bleeding. However, hysterectomy should be avoided whenever possible to preserve fertility, particularly in young women. Furthermore, postpartum hysterectomy is affected by a significant maternal morbidity, even when performed by experienced surgeons [15]. The incidence of PPH not responding to classic obstetric maneuvers and uterotonic drugs is reported to be 1.0–1.8 in 1000 deliveries [6]. After failure of uterotonic drugs, transfusion therapies and surgical measures, the management of severe hemorrhage may also include the use of recombinant human factor VIIa (rhFVIIa, NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark), a tissue factor-activated prohemostatic agent originally introduced and licensed for the treatment of patients with congenital or acquired hemophilia and antibodies against factor VIII or IX [17]. The hemostatic effect of recombinant factor VIIa, which is administered in a supraphysiologic pharmacological

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dosage, is limited to the site of injury, because it needs tissue factor to become effective in the promotion of coagulation. RhFVIIa enhances the rate of thrombin generation by directly activating factors IX and X on platelets and thus enhancing the rate of thrombin generation [12]. Despite the lack of appropriately randomized controlled clinical trials, evidence from the literature indicates that rhFVIIa has a promising efficacy in severe non-surgical bleeding or trauma and other conditions with a 0.4%–2% incidence of thrombotic complications based on published data [14, 17]. In postpartum hemorrhage, the use of this conservative treatment option has been described previously. However, to date, only case reports and small case series describing the rhFVIIa use in postpartum hemorrhage have been reported; in most cases, it was used only after postpartum hysterectomy [1, 4, 7, 24, 26]. The results of two registries (Northern European [3] and Australian New Zealand [25]) had included larger series; however, these are collected data from many different centers with different inclusion criteria and different management strategies of postpartum hemorrhage. No study so far has specifically addressed the question of whether fertility can be preserved by the use of rhFVIIa through avoiding postpartum hysterectomy; thus, all previous studies included patients who were treated with rhFVIIa only at the time or after postpartum hysterectomy has been performed [5]. The aim of the present study was, therefore, to determine the clinical value of rhFVIIa administration in the treatment of postpartum hemorrhage prior to hysterectomy with the goal to preserve fertility in a larger single center series of patients.

Materials and methods

Our prospective cohort analysis included all 22 consecutive patients from April 2004 to May 2008 with severe postpartum hemorrhage, who had been treated with rhFVIIa as a rescue therapy after unsuccessful medical and surgical uterine-preserving management at the University Hospital Bern, Switzerland. Due to the study design, this study was exempted from the institutional review board approval. In all patients, uterine preservation and avoidance of hysterectomy was the goal of rhFVIIa therapy. Included patients showed no history or evidence of known factor VIII or IX deficiency prior to the treatment. RhFVIIa was injected intravenously with a single mean dosage of 71 µg/kg bodyweight (range 34–137 µg/kg). Repeated administration within 60 min, due to insufficient efficacy, was necessary in two patients.

The clinical algorithm in postpartum hemorrhage prior to rhFVIIa treatment included uterotonic drugs, such as i.v. oxytocin, i.v. methylergometrine, misoprostol (1000 µg rectally as a single dose), i.v. sulprostone, fluid management, the substitution of erythrocyte concentrates, fresh frozen plasma (and/or fibrinogen administration) and platelet transfusion if required. Surgical interventions included the identification and repair of lower genital tract lesions, the manual and instrumental uterine revision and curettage, uterine tamponade by a balloon catheter or by surgical towels, laparotomy and uterine compression sutures (B-Lynch or Pereira sutures, Hayman suture technique, square sutures), uterine artery embolization in 1 case, and finally, if unresponsive to conservative treatments and rhFVIIa application, hysterectomy was performed. Recombinant hFVII treatment was initiated if bleeding was not controllable by medical or surgical procedures, as a last step before proceeding with a hysterectomy.

Hematologic parameters were monitored repetitively before, during and after postpartum hemorrhage treatment, and rhFVIIa therapy was initiated after given indication was confirmed by a hemostasiologist. Follow-up monitoring was individualized and included at least the following: postoperative intensive care unit surveillance, hematologic screening of hemoglobin, hematocrit, thrombin time, international normalized ratio, fibrinogen, screening of liver and kidney functions, and clinical evaluation. The hemostatic efficacy of the drug was evaluated clinically and considered good when visible bleeding cessation was noticed within 30 min following rhFVIIa administration. Posttherapeutic transfusion rates of blood products were indirect parameters for continuing bleeding and therefore for treatment failures. In order to prevent posttherapeutic clotting, a prophylactic low dose of heparin was administered during hospitalization, after thrombocyte levels reached more than 100 G/l. Patients were followed until 6 weeks postpartum to exclude thromboembolic events.

Data were anonymized for analysis. Statistical calculations including paired *t*-test and rank sum, where applicable, were performed with commercially available software (GraphPadPrism4, GraphPad Software Inc., La Jolla, CA, USA) and reached significance with $P<0.05$.

Results

During the study period, 22 patients with a mean age of 31.8 years (21–43 years) and a mean bodyweight at hospitalization of 66.90 (50–95) with a massive postpartum hemorrhage (defined as estimated blood loss >1500 mL, range 2000–15,000 mL) were treated with rhFVIIa after failure of conservative and/or surgical therapy. The mean gestational age was 38.4 weeks post menstruation (range 30–42 weeks p.m.). Patients' characteristics and delivery modes are shown in Table 1.

Uterine atony was present in 20 cases (91%), pathologic placentation (placenta increta) in two women (9%), placenta accreta in two cases (9%) whereas placenta retention was found in four patients (18%) and lower genital tract lesions in seven cases (32%). One uterine inversion (case E) was diagnosed in our patient series.

Conservative surgical treatment comprised curettage in 73% (16/22) and uterine tamponade with surgical towels or by balloon catheters in 50% (11 women). Uterine packing sutures were applied in 54% (12 cases) and operative revision and suturing of the lower genital tract was performed in 32% (7 women). In a case of surgical bleeding, the left uterine artery was embolized.

Recombinant hFVIIa was successful in stopping the postpartum hemorrhage and preserving the uterus in 20/22 patients (91%).

One woman (case L, Table 2) showed an initially reduced bleeding pattern, but continuing blood loss after medical, conservative operative therapy and rhFVIIa treatment, therefore requiring postpartum hysterectomy. After uterine resection, bleeding was stabilized.

In one intraoperative application after massive packed red blood cell transfusions, rhFVIIa was unsuccessful in stopping a surgical bleeding, therefore postpartum hysterectomy was initiated (case P). In both cases of failure of rhFVIIa treatment, an increte placenta was present.

Table 1 Patient characteristics.

	Age (years)	Weight (kg)	Age (weeks p.m.)	Gravidity (n)	Parity (n)	Type of delivery	Obstetric diagnosis
Case A	27	70	39	1	1	Secondary cesarean section	Uterine atony, monochorionic diamniotic twin pregnancy
Case B	36	62	40	2	1	Vacuum extraction	Paravaginal tear, cervical laceration, uterine atony
Case C	34	66	42	2	2	Spontaneous after induction	Uterine atony
Case D	28	59	41	2	2	Spontaneous after induction	Uterine atony, cervical laceration, placenta retention
Case E	34	62	39	1	1	Vacuum extraction	Placenta retention, inversion of the uterus, cervical laceration, uterine atony
Case F	41	72	41	1	1	Secondary emergency cesarean section	Uterine atony
Case G	33	64	42	2	2	Secondary cesarean resection	Uterine atony, tear in mesosalpinx
Case H	37	60	30	2	2	Secondary cesarean section	Chronic placental insufficiency, uterine atony
Case I	27	72	40	1	1	Vacuum extraction	Uterine atony, cervical and vaginal laceration
Case J	43	54	31	1	1	Primary cesarean section	HELLP, placenta accreta, uterine atony
Case K	31	63	42	1	1	Vacuum extraction	Uterine atony, cervical laceration
Case L	32	70	37	2	2	Primary cesarean section	Increte placenta previa
Case M	30	74	38	1	1	Secondary cesarean section	Uterine atony, tear, HELLP postpartum
Case N	21	75	39	1	1	Primary cesarean section	Uterine atony
Case O	31	70	41	1	1	Secondary emergency cesarean section	Uterine atony, uterine artery lesion
Case P	28	51	36	2	2	Spontaneous	Placenta increta
Case Q	33	50	41	3	2	Spontaneous	Uterine atony, cervical laceration
Case R	26	80	41	3	2	Vacuum extraction	Uterine atony
Case S	31	95	32	1	0	Primary cesarean section	Uterine atony, HELLP
Case T	32	70	40	3	3	Primary resection	Uterine atony
Case U	36	60	31	2	2	Secondary cesarean section	Uterine atony, placenta accreta
Case V	29	72.5	41	3	1	Secondary cesarean section	Cervical laceration, uterine atony

HELLP=hemolysis, elevated liver enzymes, low platelet count.

One woman was rehospitalized 18 days after successful rhFVIIa treatment of a uterine atony. Massive bleeding occurred again due to an incomplete placenta evacuation and was managed by conservative operative therapies (curettage and tamponade, case A) a hematologic follow-up 6 months after the last event showed a mild thrombocyte aggregation disorder without other proofs of hemophilia.

Disseminated intravascular clotting (DIC) as an acquired hemorrhagic diathesis characterized by systemic activation of coagulation was confirmed by a hematologist in each case, and was present to some degree in 18 patients at the time of treatment.

No clinical thromboembolic event occurred in our case series. Patients' history showed two women (cases S and H) with a history of central pulmonary thromboembolism, with consecutive anticoagulant medication during pregnancy. Both showed no clinical evidence for a relapse or thromboembolic complications under rhVIIa therapy. A thromboembolic event was excluded by radiologic examination in a patient after an intraoperative epileptic seizure (case M). Other adverse events comprised a transient pulmonary edema in one woman (case C), one secondary renal insufficiency (case F) and one successfully conservatively treated paralytic ileus (case V); however, it seems unlikely that there is any relation between these adverse events and rhFVIIa treatment.

The mean hemoglobin prior to rhFVIIa treatment was 70.3 g/L (40–18 g/L) with a mean hematocrit of 0.21 (0.12–0.35) and transfusion mean of 9.7 units of erythrocyte concentrates (2–18 units). After rhFVIIa injection, significantly less red blood cell transfusions (2.6 units, $P<0.001$), fresh frozen plasma substitutions (1.8 units, $P<0.001$; vs. 6.8 units pre-therapeutically) and thrombocyte transfusions (1.2 units vs. 0.2 units, $P<0.001$) were necessary (Table 2). Transfusions and rhFVIIa therapy resulted in a significant rise in mean hemoglobin to 90.8 g/L (66–120 g/L, $P<0.001$) and in mean post-therapeutic hematocrit of 0.26 (0.19–0.35, $P<0.002$). Partial normalization of coagulative values was examined approximately 24 h after rhFVIIa treatment with significant changes in mean values of fibrinogen (1.8 g/L vs 4.1 g/L, $P<0.001$), partial thrombin time (80.5% vs. 100%, $P<0.001$) and international normalized ratio (1.21 vs. 1.00, $P<0.01$) when compared to serologic screening a maximum 12 h before rhFVIIa therapy (Table 3 and 4, respectively).

Table 2 Surgical treatment and outcome after rhFVIIa application.

	Transfusions RBC/FFP/PLT		Surgical treatment	Estimated blood loss (mL)		Outcome
	Before	After rhFVIIa		Before rhFVIIa	Total	
Case A	14/10/2	4/2/-	Cesarean, 2x tamponade, curettage	7000	7000/ (+6000)	Initially good response, second uterine atony, placenta retention after 18 days
Case B	5/1/1	1/-/-	2x operative revision of the lower genital tract, tamponade	2000	2500	Initially good response, second dosage necessary
Case C	4/8/2	-/-/-	Curettage, tamponade	2400	2500	Good response
Case D	4/4/-	-/-/-	Curettage, tamponade, operative revision of the cervix reversion, B-Lynch sutures, square sutures of the uterus,	2000	2000	Good response
Case E	18/10/2	-/-/-	Revision of cervix, curettage, tamponade	n.a.	n.a.	Good response good response, secondary renal insufficiency,
Case F	17/17/3	-/-/-	Curettage, tamponade, operative revision, uterine pack sutures	3000	3000	Bladder laceration, wound infection
Case G	8/8/2	1/-/-	Curettage, revision, sutures	2800	3000	Good response
Case H	8/4/-	-/-/-	Cesarean, revision	2800	2800	Good response
Case I	17/8/1	-/-/-	Curettage, cervix-suture	2700	2700	Good response
Case J	5/3/2	1/3/-	Cesarean, revision, B-lynch sutures, curettage	4500	4500	Good response
Case K	10/10/2	-/-/-	Curettage, tamponade, cervix-revision	3000	3000	Good response
Case L	9/6/2	3/1/-	Cesarean,revision, sutures, curettage, hysterectomy p.p.	4500	6500	No response, bleeding continued
Case M	12/8/-	-/-/-	Cesarean, revision, B-lynch sutures	4250	4500	Good response
Case N	12/7/1	-/-/-	Curettage, tamponade, revision, B-lynch sutures	5100	5100	Good response
Case O	15/12/4	-/-/2	Revision, tamponade, B-Lynch sutures, embolization left uterine artery	6700	7500	Good response, surgical bleeding reduced
Case P	7/8/1	0/4/1 23/18/1	2x curettage, hysterectomy	n.a.	15000	Go response, bleeding continued
Case Q	8/6/-	-/2/-	Curettage, revision of the cervix	3000	3000	Good response
Case R	2/-/-	-/-/-	Curettage, tamponade	2000	2000	Good response
Case S	5/2/-	1/3/1	B-lynch, pereira sutures, intrauterine catheter	4000	5000	Good response
Case T	5/5/1	1/-/-	curettage, 2x intrauterine catheter, tamponade	2500	3500	Good response
Case U	2/4/-	3/-/-	B-Lynch, Pereira and uterine square sutures	2800	3000	Good response
Case V	8/8/1	4/4/-	B-Lynch, Hayman sutures, curettage	5500	6000	Good response

RBC=packed red blood cell transfusion, FFP=fresh frozen plasma, PLT=platelet transfusion, n.a.=not available.

Hematologic follow-up after 6 months was performed in five cases and revealed one factor XIII deficiency and one protein S deficiency (cases B and R). A mild thrombocyte aggregation disorder was diagnosed in one woman (case A).

Comment

Massive PPH remains one of the most common causes of maternal mortality therefore demanding precise management protocols. After failure of medical and conservative surgical measures [11], emergency postpartum hysterectomy is often unavoidable. The loss of fertility especially in women delivering the first child including an augmented mortality of preterm neonates often associated with pathologic placentation has a major psychologic impact. Depressive disorders are known to impair the quality of life of women who had to undergo emergency postpartum hysterectomy [16]. Furthermore, postpartum hysterectomy is associated with a high blood loss, a

Table 3 Hematologic findings before treatment.

	Hemoglobin (g/L)	Hematocrit (%)	Thrombocytes ($\times 10^9$/L)	Fibrinogen (g/L)	aPTT (activated partial thromboplastin time) (s)	Thromboplastin time (%)	INR (International normalized ratio)	Thrombin time (s)
Case A	77	23	64	1.56	81.6	74	1.12	11.5
Case B	59	17	104	1.59	68.2	98	1.19	12
Case C	64	19	133	1.91	40.1	99	1	9.8
Case D	71	20	68	0.52	57.6	44	1.64	35.1
Case E	68	20	68	0.89	75.1	39	1.76	14.4
Case F	77	24	79	0.97	50.9	32	1.97	17.7
Case G	71	21	110	n.a.	n.a.	79	1.16	n.a
Case H	52	16	136	2.14	41	100	1.06	23.6
Case I	63	18	86	n.a.	n.a.	91	1.08	n.a
Case J	65	19	68	1.43	41	85	1.13	15.6
Case K	118	35	85	1.82	40.5	88	1.16	12.7
Case L	48	13	49	1.32	41.5	88	1.15	13.6
Case M	72	21	218	3.96	33.8	100	1	10.2
Case N	66	22	137	1.31	49.2	100	1	13.9
Case O	40	12	33	1.24	55.2	57	1.34	13.8
Case P	66	20	97	n.a.	n.a.	100	1	n.a
Case Q	86	25	126	1.63	50.4	65	1.24	12
Case R	83	25	234	3.25	29	100	1	11.7
Case S	82	23	46	1.33	38.8	72	1.2	22.8
Case T	72	22	158	n.a.	n.a.	78	1.16	n.a
Case U	71	21	193	38.1	38.1	96	1.02	11.4
Case V	70	21	60	n.a.	n.a.	88	1.15	n.a

n.a.=not available.

need for blood transfusion, high intraoperative morbidity and postoperative complications.

Application of rhFVIIa in patients with pre-existent normal coagulation system, who experience excessive bleeding, has been explored in trauma and is increasingly used in obstetric and gynecologic indications [3, 19]. Previous reports describing the effect of administration of rhFVIIa in PPH are of limited numbers and predominantly associated with use after postpartum hysterectomy.

The results of our study – to our knowledge, the largest published so far – a single center cohort for fertility preservation by rhFVIIa, clearly suggest that rhFVIIa is effective as a second line treatment in controlling bleeding in severe PPH, and specially, in avoiding the need for emergency hysterectomy in most cases if used early enough. With an overall success rate of 90.1% (n=20/22), rhFVIIa was effective in achieving sufficient hemostasis, comparable to published reports [17].

Present metabolic acidosis in one patient with continuing bleeding (case L) might have impaired the hemostatic effect of rhFVIIa [18] (data not shown). Both failures of therapy (cases L and P) showed pathological placentation with invasion into the myometria, suggesting a possible limitation of rhFVIIa in analogy to surgical bleeding (as in case O where additional embolization of the left uterine artery was necessary) although in contrast to recently published case reports especially in combination with arterial embolization [2, 20]. Since the pharmacological mechanism of rhFVIIa is mediated via a thrombin burst and is platelet dependent, a sufficient number of platelets (e.g., >50 G/l) seems to be one prerequisite, as postulated previously [21]. The low platelet count might be an additional explanation of the missing response in case L, and eventually also in case O where additional embolization was necessary after rhFVIIa treatment.

The optimal dose of rhFVIIa is yet unknown. Our data suggest that a single dose of 70 µg/kg may be sufficient in most cases to control severe PPH in agreement with previous literature reviews [24]. According to consensus recommendations for the off-label use of recombinant factor VIIa therapy [27] a mean dosage of 71 µg/kg was capable to arrest bleeding with the lowest dosage of 36 µg/kg bodyweight.

One important drawback of this study is that it is not a randomized controlled trial; we therefore cannot exclude confounding effects of the concomitant surgical or medical treatment. However, due to known difficulties in performing randomized trials in postpartum hemorrhage, there are no such data available in the literature [9]. Nevertheless, the astonishing clinical hemostatic effect of rhFVIIa was evident in almost all cases in our series. Furthermore, in our cases, rhFVIIa treatment was given as the "last resort" before proceeding with hysterectomy as also proposed by a recently published Australian clinical guideline [29]. The treatment success of 91% to avoid hysterectomy is therefore evident even in the absence of an appropriately randomized control group. Thus, the optimal timing of its usage should be prior to hysterectomy. In agreement with other clinical trials, our data suggest that secondary effects, such as thromboembolic complications, are probably rare (<1.4%) [10, 27] even in high-risk patients. Severe PPH associated with previous thromboembolic events did not alter the safety profile in emergency use of rhFVIIa in our case series. However, due

Table 4 Hematologic findings after treatment.

	Hemoglobin (g/L)	Hematocrit (%)	Thrombocytes ($\times 10^9$/L)	Fibrinogen (g/L)	aPTT (activated partial thromboplastin time) (s)	Thromboplastin time (%)	INR (International normalized ratio)	Thrombin time (s)
Case A	92	27	39	2.24	34.6	100	1.02	13.5
Case B	81	23	71	n.a.	n.a.	100	1	n.a.
Case C	86	25	128	2.13	32.6	100	1	12.1
Case D	79	22	76	4.62	35.3	100	1	14.8
Case E	82	23	100	4.8	33.6	100	1	12.1
Case F	102	29	91	4.83	33.3	100	1	22.7
Case G	81	23	139	3.21	36.1	100	1	13.7
Case H	120	35	95	2.31	39	100	1.04	26.2
Case I	81	23	98	3.55	38.8	100	1	11.9
Case J	113	32	100	3.24	33.5	100	1	13.7
Case K	100	29	60	6.42	32.6	100	1	12.9
Case L	101	29	82	n.a.	n.a.	100	1	14.1
Case M	66	19	97	6.84	35.8	100	1	13.3
Case N	108	32	128	4.3	33.8	100	1	15.7
Case O	89	26	103	6.47	36.4	99	1	12.6
Case P	99	29	83	2.28	33.7	100	1	18.8
Case Q	120	35	114	2.4	35.2	100	1	11.9
Case R	85	25	252	3.82	29	100	1	16.9
Case S	83	25	23	3.7	38.6	100	1	18
Case T	72	21	199	2.05	38.8	100	1	17.1
Case U	77	22	230	7.62	34.5	100	1	12.5
Case V	80	23	90	n.a.	n.a.	100	1	n.a.

n.a.=not available.

to co-treatment and due to the limited case series numbers, adverse events may be underestimated. Since most reported thrombembolic events in the arterial and venous system followed the use of rhFVIIa for unlabeled indications, randomized controlled trials in PPH are needed to establish the safety and efficacy of rhFVIIa in patients without hemophilia [23].

The economic impact of rhFVIIa therapy is difficult to quantify. In our study, we did not evaluate cost-benefit analysis. According to preceding publications, rhFVIIa is cost effective in blunt trauma [27] and intracerebral hemorrhage, when avoiding 10 or more units of packed red blood cells, not calculating the benefits of prevention of multiorgan failure and live salvage [8]. However, these data do not take the costs of surgical revisions into account. Furthermore, as in the case of PPH, the costs of postpartum hysterectomy itself and the patient's benefits if hysterectomy is avoided and therefore fertility is preserved, are other important issues in the cost-benefit calculation.

The commercially available preparation of rhFVIIa (NovoSeven®) is licensed for use in hemophilic patients affected by inhibiting antibodies towards Factor VIII or XI. The use in postpartum hemorrhage is therefore off-label; this fact has to been taken into account if rhFVIIa is used for this indication.

Since rhFVIIa was able to stop PPH and preserve fertility in 91% of all treated patients, our study suggests that administration of rhFVIIa should be considered as a second-line therapeutic option of life-threatening postpartum hemorrhage in conjunction with other medical and uterine-preserving surgical interventions, in particular if preservation of fertility is warranted.

Condensation

Recombinant human factor VIIa is an effective second-line therapeutic option for life-threatening postpartal hemorrhage to avoid postpartum hysterectomy and preserve fertility after conservative medical and surgical measures have failed.

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