

Recombinant factor VIIa: use in fatal post partum hemorrhage – Indian experience case series and review of literature

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Abstract Postpartum hemorrhage is leading cause of maternal mortality and still remains a challenging condition to treat and hysterectomy may be required to control the bleeding once medical interventions fail. These strategies are not always successful and a direct approach in activating the coagulation system can be more effective and life saving. We describe here the mechanism of action of rFVIIa, review of literature and its use in 10 cases with different causes for PPH with good response.

Keywords PPH · Hemorrhage · rFVIIa · Coagulation · Bleeding · NICE registry · NovoSeven.

Introduction

Postpartum Hemorrhage remains a major complication in obstetric patients. Although maternal mortality as a result of major hemorrhage has declined in Western nations, peripartum hemorrhage remains a leading cause of maternal and fetal morbidity and mortality in both developed and developing countries. In the developing world, the risk of maternal death from postpartum hemorrhage (PPH) is approximately 1 in 1000 deliveries [1]. Depending upon the criteria used; the true incidence of PPH may vary between 3.9 to 18 % of pregnancies. It may still be an under-reported problem in Indian subcontinent where many deliveries are conducted at home and deaths are not reported.

Postpartum hemorrhage – an obstetric emergency in perspective

Pregnancy is a hypercoagulable state. Massive postpartum hemorrhage (MPPH) that might be fatal is seen with uterine rupture, placental abruption, uterine atony, placenta accreta, placenta praevia, retained placenta, coagulation defects and trauma to the genital tract. Excessive uterine bleeding seen vaginally or concealed placental abruption with large clot formation may lead to consumptive coagulopathy and disseminated intravascular coagulation (DIC). Conditions that predispose and worsen obstetrical hemorrhage belong to 4 main groups:

1. Placenta accreta/increta/percreta, placental abruption and placenta praevia.
2. Trauma during labor and delivery, uterine rupture, high parity, hyper stimulation, obstructed labor and cervical rupture.
3. Uterine atony, over distended uterus, exhausted myometrium and prolonged labor.

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4. Coagulation defects, placental abruption, severe preeclampsia, amniotic fluid embolism, intrauterine fetal death, sepsis, massive transfusion and congenital coagulopathies [2].

In a study of 763 pregnant women, who died due to hemorrhage, 141 (19%) had placental abruption, 125 (16%) uterine rupture, 115 (15%) uterine atony, 108(14%) coagulopathy, 50 (7%) placenta praevia, 44(6%) placenta accreta, 44 (6%) uterine bleeding and 32(4%) retained placenta [3].

MPPH was defined as a blood loss in excess of 1500 ml; with a drop in hemoglobin concentration of ≥ 4 g/dl and the need of ≥ 4 units of blood [4]. It can also be defined as: Blood loss of > 150 ml/min (within 20 min causing loss of more than 50% of blood volume), or sudden blood loss of > 1500 – 2000 ml. If the blood loss occurs before 24 h it is deemed early postpartum hemorrhage; after that (24 h–6 week) it is late or delayed postpartum hemorrhage. The complications of MPPH include hypovolemic shock, DIC, renal failure, hepatic failure and ARDS. Factors influencing the outcome are: underestimation of blood loss, late diagnosis of uterine rupture, undiagnosed concealed abruption, late diagnosis of retroperitoneal or intra abdominal bleeding, rapid changes of coagulation events, inability to accurately diagnose the severity of DIC and the lack of ideal hospital facility [5].

Treatment of postpartum hemorrhage

The cornerstone of the treatment of major post-partum hemorrhage (PPH) consists of medical management and/or surgery with effective transfusion therapy and uterotonic drugs. [6]

General rules

At diagnosis of PPH immediate action should be taken in the “golden hour” to replace the lost Blood volume, effective measures to control surgical cause of bleeding and correct the coagulopathy.

In the first stage external massage of the uterine fundus should be applied. At all times clinical examination must be done to exclude other causes such as: retention of placenta remnants, postpartum injury to the cervix and/or vaginal wall (hematoma), rupture of the uterus etc.

1. Pharmacological treatment with drugs like Oxitocin, Methylergometrin, Dinoprost, Sulproston, Mizoprostol etc.
2. Blood Products support:
 - Packed cell transfusion to maintain Hemoglobin 8 gm% and above.
 - FFP – 15-20 ml/kg (6-8 units), to maintain PT and APTT less than one and half times than control value.
 - Cryoprecipitate – 1-1.5 units/10 kg (8-10 units), to maintain Fibrinogen above 100 mg%.

- Platelets – RDP- 1 unit/10 kg (5-8 units) or SDP to maintain Platelet count above 50,000/ μ L

3. Desmopressin (DDAVP) or Antifibrinolytic drugs like Epsilon aminocaproic acid (EACA), Tranexamic acid (TXA) and aprotinin significantly decrease bleeding, but are not effective in major hemorrhage.
4. Surgical management: Discussion on surgical intervention will not be done here as it will be beyond the scope of this title.

Recombinant factor VIIa – novel concept in hemostasis

Recombinant factor VIIa (rFVIIa) (NovoSeven[®], Novo Nordisk A/S, Bagsvaerd, Denmark) is recombinant protein with same amino acid sequence as natural Factor VIIa. When given as IV bolus its half life is 2–3 h. It was introduced in 1996 and is licensed for the treatment of bleeding episodes in patients with congenital hemophilia A or B and who have developed inhibitors to factors VIII or IX, and in patients with factor VII deficiency or Glanzmann’s thrombasthenia with anti-GpIIb/IIIa antibodies. It has also been used as an off-label drug for intracerebral hemorrhage and trauma patients [7–9].

Mechanism of action: The availability of rFVIIa for research has enabled substantial contributions to the current concept of hemostasis. The current concept suggests that hemostasis occurs principally on two types of surfaces, the TF-bearing cell and the thrombin-activated platelet, and in two phases. The first phase, the initiation of hemostasis, occurs on the TF-bearing cell surface as a result of the exposure of TF following an injury to the vessel wall. TF is found on cells that are located in the deeper layers of the vessel wall and is normally not exposed to the circulating blood. TF is receptor for FVII and activated VII (VIIa). Following injury, TF is exposed to the circulation and forms a complex with the FVII or FVIIa on the surface of TF bearing cell. This results in limited amount of thrombin generation. This thrombin activates the co-factors VIII and V as well as platelets. Thrombin activated platelets will expose phospholipids which will further support the binding of the coagulation factors and thereby facilitate the full thrombin burst necessary for effective hemostasis. The second phase, the propagation phase, occurs on the surface of the thrombin activated platelet through complex formation between FIXa and FVIIIa (Tenase complex), and between FXa-FVa (prothrombinase complex). As a result, a full burst of thrombin is generated on the thrombin-activated platelet surface (Fig. 1). More recent evidence suggests that the supra-normal levels of rFVIIa administered clinically, causes a thrombin burst following the generation of a prothrombinase complex [10, 11].

In vitro studies have shown that compared with normal clot, the fibrin clot formed in the presence of high thrombin concentration generated by rFVIIa has a different archi-

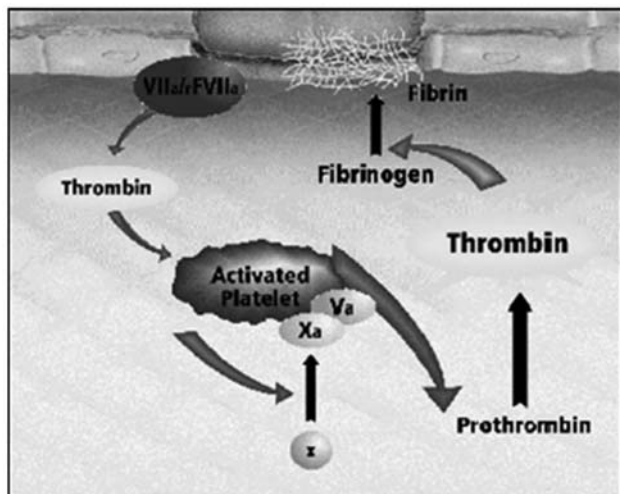


Fig. 1 Mechanism of action of rFVIIa

texture; is stronger and is more resistant to degradation by fibrinolytic enzymes [12].

In complex situations there is a risk of thrombo-embolic complications associated with the use of rFVIIa. However, in previously healthy patients with major hemorrhage, the risk seems to be low even in the presence of a DIC. Since licensing in 1995 December until Jan 2005 it is estimated that the total amount of rFVIIa released from Novo-Nordisk corresponds to 680,245 doses. Total of 123 thromboses events have been reported corresponding to 1 in 5530 standard doses of rFVIIa [13]. It is suggested that rFVIIa should be administered as early as possible: before metabolic complications develop, before signs of severe diathesis develop, to prevent severe hypoxia and organ damage. It is also important to note that before rFVIIa is administered, correction of metabolic acidosis and hypocalcaemia, prevention of hypothermia and maintaining platelet above 50,000/ μ l and fibrinogen above 100 mg/dl is essential. There are number of case reports where use NovoSeven has been shown to be effective in treating severe PPH. However, it seems unlikely that randomized controlled trials will ever be performed in patients with life-threatening PPH. Only limited data can be found in the literature regarding the use of rFVIIa in emergency obstetrical cases. The dosing is arbitrary with lack of an accepted method of monitoring the effect of rFVIIa. Normally the Prothrombin and the activated partial thromboplastin time (PT and aPTT) will shorten after rFVIIa administration, but is insufficient to ensure an effective haemostatic dose. The cases are followed on clinical data and the requirement of blood products. Most cases show success after administration of 60–120 μ g/kg of rFVIIa [14–22].

Discussion

There are two different types of postpartum hemorrhage: early and late hemorrhages. Uterine atony is the main cause

of early hemorrhage and more commonly occurs in the first 24 h after delivery. However, visual assessment underestimates the amount of blood loss in around 45% of cases thus delaying the emergency treatment, giving time for DIC to occur, which worsens the prognosis. Medical treatment and obstetric maneuvers are usually effective. When these measures are insufficient, surgery is necessary and sometimes bilateral ligation of hypogastric arteries or controlled embolization is recommended. In cases of uncontrolled bleeding, haemostatic hysterectomy is performed as a salvage therapy. Also, the efficacy of ligation of the hypogastric arteries remains controversial. The development of interventional radiology has offered a new approach for the management of postpartum hemorrhage. Many publications have showed the usefulness of the procedure, whose success rate is around 90%. However, a specific technical plateau is needed, which is far to be available at any place and at any moment. For patients delivering far away from these technical sites, limiting blood loss is crucial. Taking into consideration the above described aspects, it is worth evaluating the potential medical interest of giving rFVIIa early in the course of hemorrhage, compared to giving it as a salvage therapy after arterial selective embolization or hysterectomy in patients still bleeding, in order to avoid haemostatic hysterectomy.

Case series – our experience

We report here 10 patients with major PPH using rFVIIa. In all the cases there was good response with dose ranging from 20 to 80 μ g/kg (Table 1). During the years 2006–2007, NovoSeven[®] was used in 10 patients with massive postpartum hemorrhage, in 3 hospitals in Hyderabad. These patients were managed at a tertiary care hospital. The coagulopathy was corrected with packed cells, fresh frozen plasma, cryoprecipitate and platelets. All patients received recombinant activated factor VII (rFVIIa) intravenously, at doses of 20–80 mcg/kg and total doses of 1.2–4.8 mg.

The causes of bleeding in the 10 patients were: uterine atony-6, placenta accreta-1, Placenta percreta 2 and Post Hepatitis Coagulopathy in 1. Hysterectomy was done in 9 women and 2 patients required repeated surgery. The procedures for uterine atony and bleeding were oxytocin and prostaglandin application, laparotomy and B Lynch suture when needed. 9 out of 10 cases ended with hysterectomy. When the bleeding continued, NovoSeven[®] was given. Massive postpartum bleeding led to DIC in 6 patients. The extreme cases required massive transfusions of 3 to 25 units of packed cells, 8 to 39 units of fresh frozen plasma, upto 39 units of cryoprecipitate and 2 to 9 units of single donor or random donor platelets.

NovoSeven[®] was used and is indicated with massive postpartum hemorrhage in a fatal situation when no other treatment was available. Massive postpartum hemorrhage is an active and progressive process. The coagulopathy and

Table 1 Characteristics of the 10 parturient with Massive PPH treated with NovoSeven (rFVIIa)

Particulars	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	29	27	22	32	26	23	32	29	34	20
Weight	62.5	54	50	64	56	52.2	57	53	64	56
Wks of Gest	38	34	38	24	39	36	37	38	34	38
Type of Delivery	VD	VD	CS	CS	CS	CS	CS	CS	CS	CS
Cause of Bleeding	AT	Post Coag DIC	AP	PP	AT	AT	AT	PP	AT	AT
Interventions	Hys	Nil	Hys	Hys	Hys	Hys	Hys	Hys	Hys	Hys
No. of Operations	3	-	1	2	1	1	1	1	1	1
Total Dose of rFVIIa	4.8	2.4	2.4 2.4	4.8	2.4	2.4	2.4	3.6 2.4	1.2	2.4
Dose in microgram/ kg	76.8	44.4	48	75 37.5	42.8	45.7	42.1	67.9 45.2	18.7	42.8
No of doses	1	1	1	2	1	1	1	2	1	1
Bleeding in lit before rFVIIa	25	7	18	15	12	14	10	12	11	10
Bleeding in lit after rFVIIa	1.5	Nil	Nil	0.4	Nil	Nil	Nil	2.0	Nil	Nil
Blood products requirement Before rFVIIa										
Packed cells	25	8	19	12	10	14	11	10	17	3
/FFP	39	28	22	28	22	9	18	12	28	8
/Cryo	36	5	5	15	10	16	10	15	15	0
/Platelets	48	36	24	16	16	16	32	27	23	10
After rFVIIa										
Packed cells	1	2	1	2	Nil	4	Nil	1	1	Nil
/FFP	4	8	0	12	10	Nil	Nil	4	12	Nil
/Cryo	0	0	0	4	Nil	0	0	0	0	0
/Platelets	4	0	0	0	0	0	0	0	4	Nil

VD: Vaginal Delivery, CS: Cesarean Section, AT: Atonic uterus, AP: Abruptio placenta, PP: Placenta percreta, ARF: Acute renal Failure, Hys: Hysterectomy, MOF: Multi Organ Failure.

the degree of irreversibility of this complicated process are difficult to evaluate as is the danger to the patient. The detrimental effect of the tissue factors on coagulation enhanced by repeated and prolonged surgery can be diminished and prevented by the use of rFVIIa.

From the aforementioned cases, it would be interesting to explore in what exact type of cases rFVIIa will be useful. There is not a clear pattern in the literature, but cases of bleeding refractory to standard therapy with blood replacement products and surgical management would be most appropriate. We emphasize that in situations of severe unanticipated PPH, surgical tamponade, correction of anemia and abnormal coagulation, treatment of hypothermia and acidosis, invasive corrective measures and the administration of pharmacological agents (uterotonics) are still the most important management strategies. However, it is possible that rFVIIa may reduce the number of hysterectomies

performed in situations of severe obstetric hemorrhage refractory to other therapeutic interventions. This still leaves the question of dose and timing of rFVIIa, when used in the bleeding patient. A wide range of doses has been reported in the world literature to date, in patients with PPH.

Recombinant factor VIIa is a potent, thrombin generating, haemostatic drug. It has a proven role in the treatment of hemophiliacs. Increasingly it is being used in a number of novel settings ranging from trauma, intracerebral and obstetric hemorrhage and bleeding after cardiac surgery. Although we do not have level 1 evidence in its investigational uses many randomized studies are already underway to further explore its efficacy and safety in many of these indications.

rFVIIa proved to be an effective agent in achieving prompt hemostasis in our patients with ongoing bleeding unresponsive to the aggressive replacement of deficient

coagulation factors and correction of surgical bleeding. We believe that it may become a useful adjunct in the treatment of difficult postoperative bleeding from acquired coagulopathy. This warrants further study in these situations with large numbers of patients to establish safety and efficacy of this drug in this clinical setting.

In addition to studying the efficacy of rFVIIa, it would be worthwhile examining the cost effectiveness of this drug. This is an expensive drug (a 2.4 mg vial currently costs about Rs.80000 in India). However, if rFVIIa can be shown to reduce the number of blood transfusions required and other therapeutic interventions, then its cost would be easier to justify. Proper dosing is difficult to determine because of the wide range of doses reported. Ahonen et al. [19] generally use in their institution an rFVIIa dose of about 90–120 µg/kg IV bolus. In our case series we administered an rFVIIa dose of about 40–80 µg/kg with adequate blood products. Escalating the dose until an adequate haemostatic effect is obtained may be necessary.

NovoSeven in Critical care – Evaluation (NICE) registry is set up in India in an endeavour to capture data with respect to usage pattern of rFVIIa in varied clinical settings. This ‘Pan Haemostatic drug’ can be suggested as a first line drug at places where proper blood banking and blood product support is not available and where high end obstetrical services and interventional radiology services are deficient. In fact this product may be used to salvage the cases with massive PPH, at primary and secondary referral centres, once drug administration guidelines are established with the help of NICE registry [23].

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