Review Article

Recombinant Factor VIIa in Post-partum Hemorrhage: A New Weapon in Obstetrician's Armamentarium

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Abstract

Post-partum hemorrhage (PPH) is a life-threatening obstetric complication and the leading cause of maternal death. The usual manner for its management includes, first, noninvasive and nonsurgical methods, and, then invasive and surgical methods. However, mortality and morbidity related to PPH still remains unacceptably high, contributing to hysterectomy in at least 50% of cases. Early, effective, and preferably noninvasive treatments that can reduce maternal mortality and morbidity due to this entity are therefore essential. One of the most spectacular advancements in the control of PPH has been the use of recombinant activated factor (rFVIIa), both as initial and a life- and uterus-saving therapy. rFVIIa also reduces costs of therapy and use of blood components in massive PPH. In cases of intractable bleeding with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery. A MEDLINE search was done to review relevant articles in English literature on use of rFVIIa in PPH. Data were constructed and issues were reviewed from there. Our experience in a series of three cases of PPH, two of atonic and one of traumatic, successfully managed using rFVIIa is also shared.

Keywords: Novoseven, Postpartum hemorrhage, Recombinant factor-VIIa

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Introduction

Post-partum hemorrhage (PPH) is a life-threatening obstetric complication, which mainly occurs without warning, predictive signs or symptoms, and often in absence of predisposing conditions. Primary PPH is defined as an estimated blood loss during the first 24 hours post-partum, of more than 500 ml in vaginal delivery and of more than 1,000 ml in case of caesarean delivery. As per recent World Health Organization (WHO) estimates, of the 5,29,000 maternal deaths per year, 25.7% take place in India. Also, PPH is the most commonly reported complication and the leading cause of maternal death, responsible for almost 30% of them.[1]

Access this article online

Quick Response Code:

Website: www.najms.org

DOI: 10.4103/1947-2714.94938

Additionally, for each single maternal death, nearly 20 more endure harm to reproductive and general health. The cornerstone of treatment of major PPH consists of medical and/or surgical management with effective transfusion therapy and uterotonic drugs as first line management.[2] Once these primary conservative processes fail in arresting the bleeding, further invasive interventions which include uterine compression sutures, systemic pelvic devascularization, angiography with selective embolization, or ultimately, as a last resort, hysterectomy can be performed. However, mortality and morbidity related to PPH still remains unacceptably high even in developed countries,[3] contributing to hysterectomy in at least 50% of cases.[4] Early, effective, and preferably noninvasive treatments that can reduce maternal mortality and morbidity from PPH are therefore essential.

One of the most spectacular advancements in the control of PPH has been the use of recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark). rFVIIa was initially developed for the treatment of bleeding episodes in patients with hemophilia A or B with formation of alloantibodies

to FVIII or FIX after replacement therapy.[5] Beyond its currently recognized indications, rFVIIa has been effectively used "off label" on an empirical basis in the treatment of massive PPH which did not respond to conventional methods. Usage of rFVIIa in obstetric hemorrhage has made an impressive journey in last ten years from its first reported usage by Moscardo *et al*., who, in 2001, published the pioneer case report[6] of successful treatment of a life-threatening PPH after caesarean delivery in a non-hemophilic woman using rFVIIa. In last 10 years, there have been a number of case reports and series documenting successful treatment of PPH with rFVIIa.[7-9] We performed a MEDLINE search to review relevant articles in English literature on use of rFVIIa in PPH. Data were constructed and issues were reviewed. There are no randomized controlled trials available and for obvious reasons, it seems highly unlikely that they will ever be performed in patients with life-threatening PPH. We report our personal experience in a series of three cases, two of atonic and one of traumatic PPH, successfully managed using rFVIIa.

Our Experience

Our first case was of a primigravida with a bicornuate uterus (pregnancy in left horn) who was taken for an emergency cesarean delivery for arrest of descent at full dilatation. Intraoperatively, placenta was found adherent, which required manual removal. Post delivery, uterus was atonic despite giving uterotonics sequentially in the form of oxytocin (bolus as well as infusion), ergometrine (i/v), and carboprost (i/m as well as intramyometrial). However, on manual uterine compression, bleeding decreased and thus compression sutures were applied. Bilateral uterine and ovarian arteries were also ligated. At the same time, misoprostol 600 mcg was given per-rectally. The bleeding got arrested and the abdomen was closed. However, the total blood loss by this time was around 2 l and volume replacement was done with intravenous crystalloids and two packs of whole blood were given. Oxytocin infusion was continued. As soon as the surgery was over and the patient was to be shifted to postoperative recovery area, she started bleeding profusely per vaginum again. Abdomen was reopened and taking all points into consideration, a decision to perform hysterectomy was taken. A subtotal hysterectomy was performed. Bleeding decreased but continued, and patient had lost a total of almost 3.5 l of blood by this time. At this stage, we decided to give rFVIIa. Inj rFVIIa (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) @ 60 mcg/kg body weight of patient was given intravenously. By subjective evaluation, bleeding decreased substantially. Abdomen was closed, minimal bleeding was present per vaginum, and therefore, after 30 minutes of initial dose of rFVIIa, another dose @ 60 mcg/kg was injected. Bleeding stopped totally after 10 minutes of second dose. Another three packs of packed cells were transfused later. Patient had an uneventful puerperium after that.

Our second case was of a primigravida who had undergone a vaginal delivery with a mediolateral episiotomy, conducted by a midwife and had a PPH. She was brought under obstetrician's care almost 40 minutes post-delivery. On examination, her pulse was 118 bpm, blood pressure of 94/60 mmHg, pallor was present, and temperature was 36.6°C. Uterus was well contracted and on vagino-cervical exploration, there was a 3-cm cervical tear at 4'O clock position which was bleeding and multiple vaginal lacerations on all vaginal walls, which were actively bleeding. Uterine cavity was also explored and there were no retained products. Cervical tear was sutured and it stopped bleeding. Vaginal mucosa had become edematous and attempts to suture it caused cutting through and more bleeding. This happens many a time when there are multiple vaginal lacerations and some time has elapsed after delivery and vaginal mucosa becomes edematous. Patient had lost total almost 2.5 l of blood by this time. Volume replacement was done with crystalloids and three packs of whole blood were transfused, and patient's temperature was brought to ambient. Inj Tranexamic acid 1 g was given i/v, but had no effect on bleeding. Vaginal packing was done but the pack was soon soaked with blood and blood started oozing out from the pack. At this juncture, we decided to give rFVIIa. Inj rFVIIa was given @ 60 mcg/kg body weight and vaginal packing was removed. Bleeding decreased and after 30 minutes of injection, stopped totally. Her rest of hospital stay was uneventful.

Our third case was again of a primigravida who had a breech presentation at term. Placenta was anterior, but not adherent. After discussion, patient was unwilling to consent for trail of external cephalic version and underwent an elective cesarean delivery. Post-delivery, the uterus was atonic and bleeding profusely. Despite uterotonics given sequentially in the form of oxytocin (bolus as well as infusion), ergometrine (i/v), and carboprost (i/m as well as intramyometrial) in repeated doses, bleeding continued. Uterine compression sutures were applied and bilateral uterine and ovarian arteries were also ligated. At the same time, misoprostol 600 mcg was given per-rectally. Total blood loss was estimated to be around 2l by this time. The bleeding decreased, but continued. Volume replacement was simultaneously done with crystalloids and two packs of whole blood were transfused. At this juncture, we decided to use rFVIIa and prepared ourselves to go ahead with a hysterectomy as a last resort, in case bleeding was not arrested. Consent from patient's husband was obtained. rFVIIa in a dose of 60 mcg/kg body weight was given and patient was observed. In 20 minutes, the bleeding

got completely arrested. Patient had an uneventful recovery after that.

All the three patients in our series had an uneventful antenatal period. The patient who underwent vaginal delivery had normal labor, uneventful till the second stage. In all our patients before injecting rFVIIa, we ensured a pH of more than 7.2, platelet counts upward of 50 000/mm^3, and fibrinogen levels upward of 150 mg/dl. All of them were discharged with a hemoglobin level upward of 7 g/dl. None of them offered any complaints indicative of venous (deep vein thrombosis, superficial vein thrombosis, or pulmonary embolism) or arterial complications (myocardial infarction or ischemic stroke).

Discussion

The usual manner for treating PPH includes, first, noninvasive and nonsurgical methods, and, then invasive and surgical methods. These include but are not limited to administration of crystalloids and red blood cells, component therapy, uterine massage and uterotonic medications; uterine compression sutures, uterine and ovarian vessel ligation, hypogastric arteries ligation, and angiographic embolism of uterine/iliac arteries. Unfortunately, the overall effectiveness of such procedures to arrest hemorrhage and prevent the need for emergency hysterectomy is assessed to be only about 50%.[10] Moreover, comparatively few centers, not only in India but also across the globe, have access to the man and material resources necessary to conduct all the aforesaid procedures.

We have now treated three cases of PPH with rFVIIa. In the first case, it was used after the obstetric hysterectomy was performed. In the second case, it was used to arrest hemorrhage from multiple vaginal lacerations, which were non-suturable and the bleeding was refractory to medical management. In such cases, at times it becomes very difficult or even impossible to arrest hemorrhage. In massive, life-threatening PPH, patients often have a coagulopathic diffuse bleeding in addition to surgical bleeding. Bleeding from larger vessels may be controlled by using various surgical methods; however, the ability to control diffuse bleeding is limited and, at many a times, not feasible. Thus, administration of hemostatic drugs that can control the coagulopathic component of blood loss may reduce mortality and morbidity in such patients. rFVIIa appears to be an effective hemostatic measure in such cases, both as a adjunctive to surgical hemostasis as well as a rescue therapy where PPH is refractory to current pharmaceutical and "uterus sparing" surgical techniques. Its mechanism of action and accumulating reports in the literature as well as clinical studies suggest that rFVIIa has a potential to function as a *universal hemostatic agent* across a range of indications.[11]

In our third case, we had learnt from our previous experience and decided to use rFVIIa before performing obstetric hysterectomy. It was successful in controlling the hemorrhage and the hysterectomy, which was looking almost inevitable, was prevented. It is not sufficient to conclude that rFVIIa can prevent a peripartum hysterectomy in all such cases, because in order to demonstrate if rFVIIa is effective, randomized control trials are needed. But, because of clinical issues in this setting, interventional placebo-controlled trials in primary PPH cases are extremely difficult to perform. However, several case series and retrospective case audits are suggestive for efficacy and safety of rFVIIa in the maternal population. These cases demonstrate that rFVIIa is currently being administered both as initial therapy and as a life- and uterus-saving therapy in women with life-threatening primary PPH.[12]

rFVIIa induces hemostasis at the site of injury. Its mechanism of action includes the binding of factor VIIa to the exposed tissue factor (TF)-dependent pathway and, independently of TF, activation of factor X directly on the surface of activated platelets localized to the site of injury.[13] Also, therapeutic effect of rFVIIa is due in part to its ability to overcome the inhibitory effect of physiologic FVII on FVIIa: TF-initiated thrombin generation.[14] At pharmacological concentrations, rFVIIa also directly activates factor X on surface of locally activated platelets and helps generate thrombin and fibrin. rFVIIa does not bind to resting platelets. Therefore, the effect of high-dose rFVIIa is localized to the sites of vessel injury only.[15] rFVIIa is eliminated following linear kinetics with a faster clearance and a shorter half-life when rFVIIa is administered for bleeding episodes compared with non-bleeding indications. Thus, when used to arrest bleeding, duration of action may by shorter. This may be related to consumption through complex formation with exposed TF at the site of vascular damage and with phospholipids exposed on the activated platelets.

The best available indicator of rFVIIa efficacy is the arrest of hemorrhage judged by visual evidence, hemodynamic stabilization, and reduced demand for blood components.[16] There is currently no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa, which is judged subjectively. Safety analyses demonstrate that rFVIIa is associated with very few treatment-related adverse events and is very well tolerated. Data accumulated from its use in thousands of patients worldwide for various indications have brought out that incidence of non-serious adverse events is 13% and serious adverse events are less than 1%.[17] Aledort calculated that the risk of rFVIIa-related thrombosis is 25 per lakh infusions.[18] Among the non-serious side effects are pain at the infusion site, fever, headache,

vomiting, changes in the blood pressure, and skin-related hypersensitivity reactions.

rFVIIa is a recombinant product and is not subject to paucity of blood. It has no human protein and carries no risk of viral transmission. It causes localized hemostasis and has low thrombogenicity. It carries a very low risk of anaphylaxis, has no anamnestic responses, and is an effective drug during and after surgery. However, it has a short half-life and may require frequent, repetitive dosing. It is also not 100% effective. It has no measurable laboratory parameter for efficacy, which is judged only subjectively. It requires a venous access. Its high cost is one of the major drawbacks in its more liberal and frequent usage.

However, it is pertinent to bring out that rFVIIa also reduces costs of therapy and use of blood components in massive PPH. This statement derives power from studies in nations where cost effectiveness of man and material resources is calculated aggressively. In UK, mean cost of blood components used in a single case is £. 6255, while rFVIIa cost for every patient in treatment is £. 3655.[19] In Italy, a single bolus of rFVIIa 60 µg/kg economically corresponds to cost of 14 PRBC.t[9] Ahonen and Jokela reported from Finland that at their institution, the cost of a single dose of rFVIIa is similar to that of transfusion with 50 units of red blood cells, an embolization procedure, or Intensive care unit treatment for 2 days.[8]

We believe that in situations of intractable PPH, and where a hysterectomy is otherwise not indicated, administration of rFVIIa ought to be contemplated before performing a hysterectomy. We also recommend administration of rFVIIa as soon as possible in few special situations like when no blood is available; in patients with acquired hemophilia, before packing of the uterus or pelvis, before considering surgical procedures like peripartum hysterectomy or laparotomy (especially in cases of vaginal delivery). In cases with actively bleeding multiple vaginal lacerations, especially in patients who are brought to an obstetrician's care some time after delivery and the vaginal mucosa has become edematous and is not amenable to hemostasis with suturing, rFVIIa should be considered early in management before patient's condition worsens and she starts slipping out of hands. Indeed in India, where relatively a major percentage of deliveries are handled by TBA and midwives, and at centers where the available manpower resources who may not have expertise in hemostatic suturing techniques, it is important that rFVIIa must be made available. All stakeholders, public as well as private, in women's healthcare, must take this responsibility together to make this drug available at such centers for usage in life-threatening PPH. Although not very relevant in India, but in women who do not accept blood or blood product transfusions (e.g., Jehovah Witnesses), rFVIIa indeed can be one of the very few life/uterus-saving treatments available.

Before administering rFVIIa, hemoglobin levels should be preferably above 7 g/dl, international normalized ratio <1.5, and platelet levels above 50 000/cumm. Fibrinogen levels of a minimum of 100 mg/dl, preferable more than 150 mg/dl must be ensured before administration of rFVIIa. In case these parameters are deranged, they must be corrected by using appropriate therapy before rFVIIa administration. Also, correction of the pH to ≥7.2 is recommended before rFVIIa administration because efficacy of rFVIIa decreases at a pH ≤7.1. If required, bicarbonate may be used to elevate the serum pH. Furthermore, body temperature should be restored to physiological values if possible, although rFVIIa retains its activity in the presence of hypothermia [Table 1]. Therefore, it is recommended that decision to use rFVIIa should be taken in time during management of PPH before metabolic complications develop and before the symptoms of severe thrombocytopathies, hypoxia, and organ injury appear.

Conclusion

The analysis of our cases clearly shows that rFVIIa was an effective hemostatic drug, which significantly decreased bleeding and led to the rapid stabilization of our patients' conditions. We noted in our third case the contraction

Table 1: Pre-requisites for using rFVIIa

Hemoglobin levels	>7 g/dl	
International normalized ratio	<1.5	May be corrected using FFP @ 10-15 ml/kg
Fibrinogen levels	Minimum of 100 mg/d	1. Preferable levels of more than 150 mg/dl 2. May be corrected using cryoprecipitate @ 1–2 units/10 kg (1 unit/10 kg raises fibrinogen levels by approx. 50 mg/dl)
Platelets levels	At least above 50,000/cumm	May be corrected by giving platelet therapy
pH	≥7.2	Bicarbonate may be used to elevate the serum pH, in case of acidosis
Body temperature	Preferably within physiological values	rFVIIa retains its activity in the presence of hypothermia

of the uterus after the drug administration in a patient who had qualified for hysterectomy shortly before the drug was administered.

PPH has a veritable equal opportunity occurrence because majority of the women who experience it have no discernable clinical risk factors. However, it is not an equal opportunity killer. A poor and anemic, malnourished woman who delivers far away from a well-equipped medical center will die from it, whereas those who are privileged enough to deliver in a well-equipped and staffed medical center will most likely survive. It is so because the later will not suffer delays. They will not suffer delay in the decision to recognize a complication and seek help; they will not suffer delay in accessing transportation; and neither delay in receiving adequate and comprehensive care upon arrival.

Shah Jahan built Taj Mahal in memory of his wife, Mumtaz, who died of PPH during giving birth to her fourteenth child in 1630.[20] Around the same time, another country in another part of the world was taking a different approach. Sweden in 1663 established the Collegium Medicum. It was the Swedish clergy who took the lead and created an information system, which in 1749 provided the first national vital statistics registry, following which within next eight years, a national training program was standardized for midwives in all hamlets of Sweden. It resulted in a comprehensive community midwifery system, with an obstetrician back up and outcome reporting; and is considered responsible for reducing the maternal mortality in Sweden to almost one fourth from years 1751 to 1900. Even today, Sweden has one of the lowest maternal mortalities in the world. People who visit Taj Mahal are mostly oblivious of the fact that how often around the world the event symbolized by this monument still occurs in the shadows of a woman's blood-soaked floor or in the helpless eyes of a primary healthcare center staves. It is high time that we take a decision that we want more Taj Mahals as monuments to hardship and suffering or take effective and efficient steps to avoid it. As Mamoud Fathalla, ex-FIGO President said in the world congress at Copenhagen in 1997 "Women are not dying because of a disease we cannot treat. They are dying because societies have yet to make the decision that their lives are worth saving." It is time we need to take decisions.

We need to prevent PPH in the first place, but if it happens, then to aggressively manage it with all what is available in our armamentarium. Aim of management should be to save every drop of blood, because with every additional drop of blood lost, the condition of the patient worsens and enters a vicious cycle of hemorrhage, coagulopathy, and hypothermia. Many a times, patients are lost with a too little done, too late. Therefore, it is important that further studies are done on this new weapon, which is now available in the obstetrician's armamentarium to give it its rightful place as a life-saving and uterus/fertility-sparing drug in management of PPH.

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How to cite this article: Magon N, Babu KM. Recombinant factor VIIa in post-partum hemorrhage: A new weapon in obstetrician's armamentarium. North Am J Med Sci 2012;4:157-62.

Source of Support: Nil. **Conflict of Interest:** None declared.