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Original Research Article

Role of Recombinant Activated Factor VIIA (NOVOSEVEN) in the Management of Refractory Post Partum Haemorrhage: A Prospective Observational Study

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Conflict of interest: Nil

Abstract:

Background: Despite advancements in healthcare, Post Partum Haemorrhage is a life-threatening obstetric complication and continues to be significant cause of maternal morbidity and mortality. Globally, PPH accounts for about 35% of all maternal deaths. The prevalence of PPH is 2-4% following vaginal delivery and 6% after caesarean section. The cornerstone of the treatment of severe PPH consists of medical management or surgical interventions with effective transfusion therapy and uterotonic drugs. However, in critical conditions the achievement of haemostasis and reversal of coagulopathy becomes more difficult. Here we are sharing an experience of 105 cases of PPH with different causes of PPH treated with new non-invasive advancement, recombinant factor 7 in PPH.

Methods: This was a prospective observational study at Patna Medical College and Hospital, Patn (Bihar) from Dec 2023 to Jan 2026.

Results: Out of 105 cases clinical response to rFVIIa (defined as bleeding decreased or stopped post administration) was seen in 92/105 (87.6%) patients. There was mortality of 7 patients. So, the total mortality rate was 6.6% in our study.

Conclusions: PPH rapidly progress and is strongly associated with the development of Disseminated intravascular coagulation (DIC). Delayed correction leads to increase in maternal deaths. Early administration of recombinant activated factor VII proved effective in controlling bleeding, reduced amount of blood loss, decreased requirement of blood products and preventing unindicated postpartum hysterectomy after conservative medical and surgical methods are failed. Although some studies showed the risk of Thromboembolism (TE) with use of factor VII, the safety analysis indicated that there was low to no increased incidence of TE associated with rFVIIa treatment in pregnant patient and should be reserved for severe PPH, the benefits often outweigh the risks.

Keywords: Recombinant factor VIIa, DIC, PPH, Novoseven.

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Introduction

Post partum haemorrhage is a life threatening obstetric complications and is the primary factor contributing to maternal mortality. Globally, PPH accounts for about 35%of all maternal deaths. The prevalence of PPH is 2-4% following vaginal delivery and 6% after caesarean section. Traditionally, postpartum haemorrhage (PPH) is defined as exceeding 500 ml of estimated blood loss with vaginal delivery or more than 1000 ml with caesarean delivery. In 2017, the American College of Obstetrics and Gynaecology redefined this, stating that the current definition is a total blood loss exceeding 1000 ml accompanied by signs and symptoms of hypovolemia within 24 hours after the birth, irrespective of the delivery method [1,2]. Indeed any bleeding that results in or even perceived could result in hemodynamically instability, if untreated, must be treated energetically as PPH. Primary postpartum haemorrhage refers to bleeding that takes place within the first 24 hours following delivery, whereas secondary postpartum haemorrhage is defined as bleeding that happens between 24 hours and 12 weeks after delivery [3]. PPH occurring within 24hrs of delivery is one of the most difficult challenges for obstetrician everywhere. Currently, the most frequent causative

factor for severe PPH are uterine (70- 80%), other include placental tissue retention (10-30%), uterine trauma & laceration of cervix& vagina (15-20%), coagulopathy 1%. The keystone of management of PPH entails first non invasive and nonsurgical methods and then invasive and Surgical methods. Prompt management with fluid and blood transfusion and uterotonic drugs is the first line therapy.[4] If these are unable to control bleeding, balloon tamponade, more drastic and invasive intervention such as uterine compression suture, bilateral uterine artery ligation internal iliac artery ligation and final last resort, hysterectomy can be performed.

One of the most recent and novel advancements in the management of PPH has been the use of Human recombinant activated factor VII (rFVIIa).

Generic name: **Eptacog alfa (activated)**

Brand name {**Novoseven**} 1mg (50KIU) powder and solvent for injection [20]

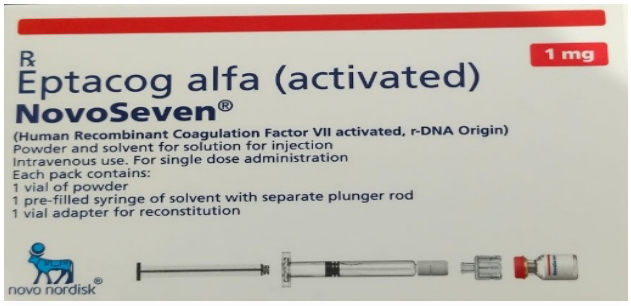


Figure 1

It was initially developed for the treatment of bleeding episodes in patient with Haemophilia A or B, Glanzmann thrombasthenia ,congenital FVII deficiency [5]. Earlier beyond recognized indications, rFVIIa has been effectively used 'off label' on an empirical basis in the treatment of massive PPH. The first successful case was reported in 2001 in a parturient without haemophilia who developed intractable, life threatening PPH as a consequences of disseminated intravascular coagulation , liver dysfunction and renal failure [6]. Indian health authority, Central Drugs Standard Control Organisation (CDSCO) approved rFVIIa (Eptacog alfa) 'for treatment of severe PPH when uterotonics are insufficient to achieve haemostasis' in 2022. As per approval, rFVIIa can be considered any time after failure of uterotonics to arrest the bleeding in the patient with severe PPH .In complex situation there is a risk of thromboembolic complications associated with the use of rFVIIa. (FOGSI- FOCUS-FACTOR-VII).[7]

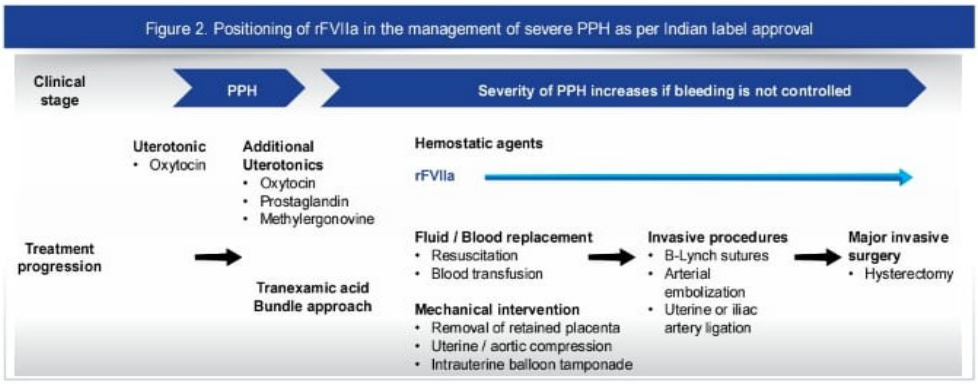
Dose Range and Interval: The recommended dose range for the treatment of bleeding 60-90 µg/kg body weight administered by intravenous bolus injection.[8]

Peak coagulant activity can be expected at 10 min after novoseven administration. A second dose can be administered based on the clinical response of the individual patient . It is recommended that in case of insufficient haemostatic response second dose can be administered after 30 min.

Shelf- life: the shelf life of the product is 36 months when the drug products is store below 25 degree Celsius.

Contraindication: hypersensitivity to the active substances or to any of the excipients.

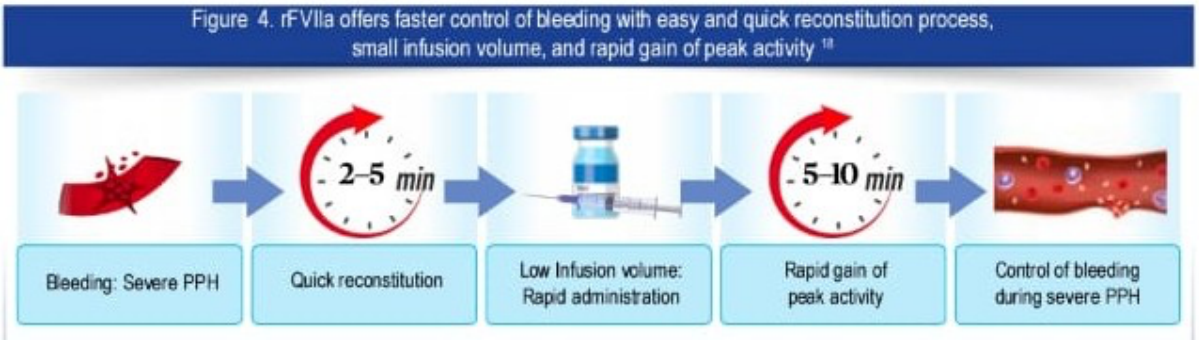
Mechanism of Action: Novoseven contain activated recombinant coagulation factor VII. The mechanism of action include: **a)** localised action at the site of injury binding of VIIa to exposed tissue factor and activated platelets are present. **b)** Initiation of coagulation cascade when rFVIIa binds to TF leading to the generation of thrombin. **c)** Generation of thrombin bursts: given in pharmacological dose, rFVIIa directly activates factor X directly on the surface of activated platelets, localised at the site of injury independently of tissue factor. this results in the conversion of the prothrombin into large amount of thrombin (thrombin bursts) independently of tissue factor**. d)** thrombin bursts leads to the formation of a stable haemostatic plug at the site of vascular injury which control bleeding and prevent further blood loss.



"International and local guidelines have been developed for the management of PPH, there are variations across the guidelines but they follow a similar escalation protocol"

Figure 2

Rapid and safe initiation of treatment with rFVIIa: administration process of rFVIIa begins with reconstituting the drug, typically taking 2-5 mins, leading to prompt response in patients with severe PPH. Low volume of only 5 ml facilitates rapid administration. When administered as iv bolus, rFVIIa reaches its peak activity within 5-10 mins.



Adverse drug reaction are pyrexia, rash, venous thromboembolic events, pruritic and urticaria and decreased therapeutic response.

Pre- requisites before using rFVIIa. Maintenance of adequate fibrinogen concentration and platelet count is recommended to optimize the benefits of Eptacog alfa(activated) [9].

Haemoglobin level	>7g/dl	
International normalized ratio	<1.5	
Platelets	>50000/m3	
pH	No acidosis (>7.2)	In case of acidosis bicarbonate can be used to elevate the serum pH.
Body temperature	Core body temperature > 35degC	Although rFVIIa retains its activity in the presence of hypothermia.
Fibrinogen level	1-2g/L	

However , it is not mandatory to maintain these parameters, and the use of rFVIIa can be considered on the basis of patient's condition and clinician decisions.

Methods

Data collection: This was a prospective observational study conducted at PATNA MEDICAL COLLEGE AND HOSPITAL PATNA (BIHAR) from DEC 2023 to JAN 2026. Data were obtained by review of patients' case notes and laboratory records. Here we are sharing an experience of 105 cases of severe PPH with different causes of PPH treated with new non-invasive advancement, recombinant factor 7 in PPH. Details of patient age, parity, gestation, mode of delivery, causes of PPH and additional measures taken to achieve haemostasis were recorded. Case notes were examined for any reported thrombotic events occurring within 7 days of administration of rFVIIa.

Statistical Analysis: Coagulation parameters were analysed using Wilcoxon signed rank test for paired nonparametric data. A p value of <0.05 was considered to be significant

Results

Table 1 is showing patients demographics. 105 patients received rFVIIa for major obstetric haemorrhage over 2years 2months period between Dec 2023 and Jan 2026. Median age was 25 years (range: 18-44 years). Among 105 patients 60 were referral cases.

Table 1: Demographic details

Age	**Number of patients**	**Percentage**
<30yrs	83	79%
>30 yrs	22	20%
Parity		
Primi	42	40%
Multi	63	63%
Gestational Age		
Term	73	69.5%
Preterm	32	30%

Table 2: depicts mode of delivery 48 patients by cesarean section and 52 by vaginal birth , 5 special cases were of post D&E in whom rFVIIa needed.

Mode of delivery	**Number of patients**	**%**
Vaginal delivery	52	49.5
LSCS	48	45.7
Post D&E	05	4.7

Table 3, tells indications for the use of rFVIIa were as follows: 60 atonic PPH, 8 traumatic PPH, 13 were due to coagulation disorder, 4 retained tissue(sec PPH). Remaining 18 cases were having combined indication in which 7 atonic + traumatic PPH, 8 atonic + coagulation disorders, 3 traumatic + coagulation disorders.1 case of post S&E of molar pregnancy.

Table 3:-

Causes	no. of cases	%
Atonic PPH	60	57%
Traumatic PPH	08	7.6%
Coagulation defects	13	12.3%
Retained tissue(sec PPH)	06	5.7%
Atonic +Traumatic PPH	07	6.7%
Atonic + Coag.defect	08	7.6%
Traumatic + Coag. defect	03	2.8%

Dosing and timing of administration of rFVIIa: All patients received the recommended dose of rFVIIa of 90 µg/kg. 13 patients received (1 mg) dose of rFVIIa, 2 patients received 1 dose of (2 mg) 20-30 minutes apart. 1 patients received 2 doses of (3 mg) 48 hrs apart. Remaining 89 patients received 1 dose of (3mg).

A clinical response to rFVIIa (defined as bleeding decreased or stopped after post administration) was seen in 92/105 (87.6%) patients.

Additional measures taken to achieve haemostasis: Prior to rFVIIa administration, additional measures to control blood loss included blood product support, uterotonic agents, antifibrinolytic agents, balloon tamponade, B-lynch suture, and vessel ligation. In 36 cases ballon tamponade was done. Surgical intervention were taken before administration of rFVIIa B lynch done in 9 cases , bilateral uterine artery ligation in 3 cases. Hysterectomy was performed in 5 patients and 2 bilateral uterine artery ligation & 2 Internal iliac artery ligation were done after the administration of rFVIIa.

Table 4: shows additional measures taken to achieve haemostasis before and after administration of rFVIIa.

Intervention before recombinant FVIIa	**Number of patients**	**%**
Ballon tamponade	36	34.2
B lynch	09	8.5
Bilateral uterine artery ligation	03	2.8
Internal iliac artery ligation	00	0

Intervention after recombinant factor VIIa

Bilateral uterine artery ligation	02	1.9
Internal iliac artery ligation	02	1.9
Hysterectomy	05	4.7

Mortality: Out of 105 pts there is mortality of 7 patients. All 7 of these patients were referred from periphery with severe PPH in moribund condition. So, the total mortality rate was 6.6% in our study.

Discussion

In this study, we found rFVIIa to be a life-saving drug in patients with massive PPH and administration can be considered before resorting to any surgery in case of severe PPH when hysterectomy is not otherwise indicated.

Efficacy of recombinant factor VIIa: Several studies have demonstrated the potential efficacy of rFVIIa in controlling life threatening PPH. In our study, there was reduction in blood loss in 87.6 % after administration of factor VII, 4.7% of cases had hysterectomy. Similar results were observed in a study by Phillips L et al [10] where rFVIIa administration in severe PPH showed significant reductions in blood loss and cessations of bleeding in 76% of the cases, hysterectomy was avoided in 79% of cases. Bouma et al [11] in these study it concluded that rFVIIa can be effective in reducing bleeding as well as preventing the need for an emergency hysterectomy [11]. In a study by Huber et al [12] says that administration of rFVIIa proved effective in postpartum haemorrhage after conservative medical and surgical intervention failed. Some of the Indian evidences are: Singi et al [13] in these study it was proved that rFVIIa to be an effective agent in prompt correction of massive PPH which was refractory to aggressive transfusion of coagulation factors, it contributed significantly to curtailed the bleeding. Magon et al [14] reported successful management of PPH and its administration can be considered before any surgery and preventing unnecessary hysterectomy. Clark et al [15] believe it is important to avoid using rFVIIa as a drug of 'last resort'. Infact, the patient with severe PPH would by this stage be so metabolically compromised that no therapy would reverse their decline, and rFVIIa might be of no value.

Reduction in need for surgical interventions: In a retrospective review by bouma et al [11] the use of rFVIIa in 27 PPH patients led to the cessation of bleeding in 24 patients, and successfully prevented hysterectomies in 76%. Similarly in our study out of 105 patients only 5 patients required hysterectomy. It suggests that rFVII could play a role in uterine preservation, which is a crucial outcome for a woman childbearing age. It concluded that rFVIIa can be effective in reducing bleeding as well as preventing emergency hysterectomy. A retrospective study conducted by Barillari et al [16] treatment with rFVIIa was associated with improvements in haemostatic parameters, a decreased need of blood transfusion products, and fewer medical and surgical intervention in patient with PPH. Similar conclusion was made in the study Huber et al [12], Colucci G et al [17] and Salman et al [18] that the administration of rFVIIa proved effective in preventing postpartum hysterectomy after conservative medical and surgical methods failed.

Safety and thromboembolic side effects: when Novoseven is administered to patients outside approved indications, arterial thromboembolic events are common (1/100 to <1/10). In our study, no adverse thromboembolic events were noted. In a study by Deedler et al [19] thromboembolic events occurred in 1.5% of cases following rFVIIa exposed women & 1.6% in non-exposed women. The safety analysis indicated that there was no increased incidence of Thromboembolic events. According to the document published by European experts, there is no scientific evidence suggesting of increased risk of thromboembolic events after using rFVIIa in patients with severe PPH. This low incidence concludes that while the use of rFVIIa should be reserved for severe PPH, the benefits often outweigh the risks. So even if the pregnant patients develops TE event after receiving rFVIIa, it could be due to underlying hypercoagulable state of pregnancy.

Cost-effectiveness: rFVIIa also reduces costs of therapy and use of blood components in massive PPH.

There are some limitations of study. The absence of control groups in these studies makes it difficult to definitively attribute improvements in patient outcomes to rFVIIa, as opposed to other interventions. Impact on blood transfusion before & after administration of rFVIIa is not included. Patient with PPH with variable causes were included in the study and response may differ depending on the underlying aetiology

Conclusion

Despite advancements in healthcare, obstetric Post Partum Haemorrhage continues to be significant cause of maternal morbidity and mortality, it rapidly progress and is strongly associated with the development of Disseminated intravascular coagulation (DIC). Delayed correction leads to increase in maternal deaths. Early administration of recombinant activated factor VII proved effective in controlling bleeding, reduced amount of blood loss, decreased requirement of blood products and

preventing unindicated postpartum hysterectomy after conservative medical and surgical methods are failed. Pregnancy is a hypercoagulable state & it increases the risk of Thrombosis 4-fold to 5-fold compare to non-pregnant state. Although some studies showed the risk of Thromboembolism (TE) with use of factor VII, the safety analysis indicated that there was low to no increased incidence of TE associated with rFVIIa treatment in pregnant patient and should be reserved for severe PPH, the benefits often outweigh the risks. The primary reason for safety profile is mainly because of its mechanism of action, as it acts locally only at the site of injury and does not activate systemic coagulation. So even patient develops TE after receiving rFVIIa, it may not be related to rFVIIa. It could be due to underlying hypercoagulable state of pregnancy.

However, rFVIIa has shorter half-life and few repetitive dose are few of its limitation. It has no measurable lab parameter for efficacy, which is judged only subjectively. Its high costs is one of the major drawbacks in its more liberal and frequent usage especially in private setups. [14]

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