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Original Research Article

Role of recombinant factor 7 in PPH: a new weapon in obstetrician's armamentarium

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ABSTRACT

Background: Post-partum hemorrhage (PPH) is a life-threatening obstetric complication and the leading cause of maternal death. It is currently managed mainly through surgical interventions with simultaneous transfusion of blood and blood-derived. However, in critical conditions the achievement of hemostasis and reversal of coagulopathy becomes more difficult. Here we are sharing an experience of 41 cases of severe PPH with different causes of PPH treated with new noninvasive advancement, recombinant factor 7 in PPH.
Methods: This was a prospective observational study at Pannadhaya Rajkiya Mahila Chikitsalya Udaipur (Rajasthan) from May 2023 to December 2023. Here we are sharing an experience of 41 cases of severe PPH with different causes of PPH treated with new noninvasive advancement, recombinant factor 7 in PPH.
Results: Out of 41 cases clinical response to rFVIIa (defined as bleeding decreased or stopped at 1 hour post administration) was seen in 26/41 (63%) patients. There was mortality of 5 patients. So, the total mortality rate was 12% in our study.
Conclusions: Obstetric hemorrhage can progress rapidly and is strongly associated with the development of disseminated intravascular coagulation (DIC). Delayed correction of DIC is associated with a significant increase in morbidity and mortality. Rapid correction of coagulopathy with ongoing regular monitoring of coagulation status is often difficult to coordinate in the setting of acute life-threatening obstetric hemorrhage. Factor VII helps in haemostasis.

Keywords: DIC, PPH, Recombinant factor VIIa

INTRODUCTION

PPH is the primary factor contributing to maternal deaths globally. Every year, approximately 14 million women suffer from PPH, leading to nearly 70,000 maternal fatalities worldwide. Traditionally, postpartum hemorrhage (PPH) is defined as exceeding 500 ml of estimated blood loss with vaginal delivery or more than 1000 ml with cesarean delivery. In 2017, the American College of Obstetrics and Gynecology 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]

Primary postpartum hemorrhage refers to bleeding that takes place within the first 24 hours following delivery, whereas secondary postpartum hemorrhage is defined as bleeding that happens between 24 hours and 12 weeks after delivery.[3] Patients experiencing significant, life-threatening postpartum hemorrhage frequently exhibit 'coagulopathic' widespread bleeding. While surgeons can manage bleeding from larger vessels through various procedures, controlling diffuse bleeding is often limited and, in many situations, not possible. Therefore, administering hemostatic agents that can manage the coagulopathic aspect of blood loss may lower mortality and morbidity in these patients. Various studies currently indicate that rFVIIa is a safe and effective hemostatic

intervention in severe obstetric hemorrhage.[4-7] It can serve both as an additional treatment to surgical hemostasis and as a 'salvage' or 'rescue' option when postpartum hemorrhage does not respond to existing pharmaceutical and 'uterus sparing' surgical methods.[8] In this study, we present our experience with 41 cases of severe PPH caused by various factors, all treated with the innovative noninvasive approach of recombinant factor 7 in PPH.

Mechanism of action

rFVII acts locally at the area of vascular damage, where tissue factor becomes exposed and activated platelets are present. The attachment of factor VIIa or rFVIIa to tissue factor starts the coagulation process, producing minimal quantities of thrombin. At pharmacological levels, rFVIIa directly triggers factor X on the surface of activated platelets, leading to a surge of thrombin.

The thrombin surge results in the creation of a stable hemostatic plug that manages the bleeding.[9,10]

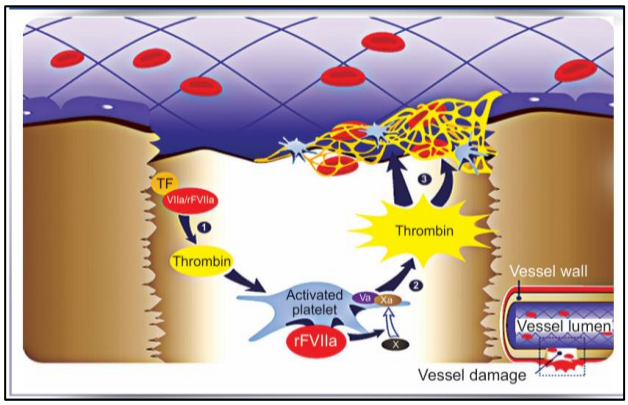

Figure 1: Mechanism of action of rFVIIa.

Administration of rFVIIa for major obstetric haemorrhage was according to a regional consensus protocol. rFVIIa was indicated if significant bleeding (at an estimated rate of greater than 200 ml/hour) continued despite optimal medical/surgical measures and blood component replacement therapy. A dose of 90 µg/kg was recommended, with a second dose 3 hours later if an initial response was not obtained.[11]

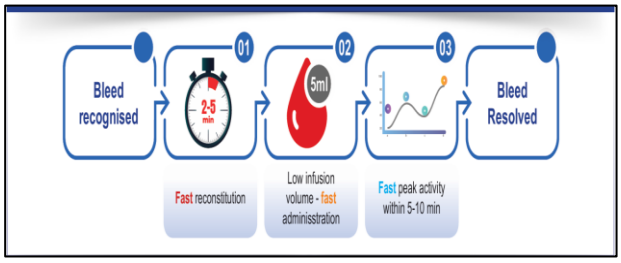

Figure 2: Administration to bleeding stop time.

METHODS

Data collection

This was a prospective observational study conducted at Pannadhaya Rajkiya Mahila Chikitsalya associated with RNT medical college, Udaipur (Rajasthan) from May 2023 to December 2023. Data were obtained by retrospective review of patients' case notes and laboratory records. Here we are sharing an experience of 41 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, dose of rFVIIa and number of doses administered, and additional measures taken to achieve haemostasis were recorded. Clinical response (bleeding unchanged, bleeding decreased, or bleeding stopped) was assessed subjectively by the attending obstetrician 1 hour after the first dose of rFVIIa. Laboratory results (Hb, platelet count) and details of blood components transfused 24 hours before and after rFVIIa administration were noted. Case notes were examined for any reported thrombotic events occurring within 7 days of administration of rfactor VII.

Statistical analysis

Coagulation parameters and blood component use pre and post rFVIIa administration 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. 41 patients received rFVIIa for major obstetric haemorrhage over 6-month period between May 2023 and December 2023. Median age was 26 years (range: 18-38 years). Among 41 patients 30 were referral cases.

Table 1: Demographic profile.

Age	Number of patients
18-25	13
26-35	25
>35	4
Parity	
Primi	8
Multipara	33
Gestational age	
Preterm	18
Term	23

Table 2: Mode of delivery.

Mode of delivery	Number of patients
Caesarean section	19
Vaginal birth	22

Table 2 depicts mode of delivery 19 patients by cesarean section and 22 by vaginal birth in whom rFVIIa needed.

Table 3: Indication of r factor 7a use.

Causes of PPH	Number
Atonic	33
Trauma	18
Retained placenta	2
Coagulopathy	5
Atonic + trauma	15

Table 3 tells indications for the use of rFVIIa were as follows: 33 atonic PPH,18 traumatic PPH, 5 were due to coagulation disorder. Used for complications such as 5 cases ruptured uterus, 1 case abdominal pregnancy, 1 case of scar ectopic.

Dosing and timing of administration of rFVIIa

All patients received the recommended dose of rFVIIa of 90 µg/kg. 15 patients received 1 (1 mg) dose of rFVIIa, 18 patients received 1 dose of (2 mg) and 7 patients received 2 doses (3 mg) 20-30 minutes apart.

Table 4 is showing there was reduction in blood products use after administration of rFVIIa.

Table 4: Number of administered products before and after rFVIIa.

Blood products replacements	Before	After
PCV	71	56
Platelet concentrate	49	32
FFP	97	49

Response to rFVIIa

A clinical response to rFVIIa (defined as bleeding decreased or stopped at 1 hour post administration) was seen in 26/41 (63%) patients. The median number of units of blood components transfused following rFVIIa was observed to be lower than before rFVIIa (Table 4).

Additional measures taken to achieve haemostasis

Prior to rFVIIa administration, additional measures to control blood loss included blood product support, uterotonic agents, antifibrinolytic agents, uterine packing, insertion of, B-lynch suture, and vessel ligation. Hysterectomy was performed in 15 patients prior to (1 patient) or concurrent with (3 patients) the administration of rFVIIa. Following the administration of rFVIIa, additional measures were required to achieve haemostasis in 7 patients. In 11 patients concurrent bilateral uterine A. ligation, in 10 pts bilateral internal iliac ligation was performed. In 2 patients compression sutures were taken.

Table 5: Additional measures taken to achieve hemostasis before and after administration of rFVIIa.

Surgical intervention before factor VII	No. of patients	Surgical inetervention after factor VII	No. of patients
Baloon tamponade	1	Compression sutures	1
Hysterectomy	1	Hysterectomy	14
Uterine artery ligation f/b internal iliac ligation	1	Internal iliac ligation	2
Ineternal iliac ligation	7	Intrauterine packing	1
Laparotomy for ruptured uterus	3	Vaginal packing	2
Uterine artey ligation	8	Uterine artery ligation	1
Grand Total	21	Grand Total	24

Table 5 shows additional measures taken to achieve haemostasis before and after administration of rFVIIa.

Mortality

Out of 41 pts there is mortality of 5 patients. 5 of these patients were referred from periphery with severe PPH in moribund condition. So, the total mortality rate was 12% in our study.

DISCUSSION

In this study, we found rFVIIa to be a life-saving drug in patients with massive PPH.

Efficacy of recombinant factor VIIa

Several studies have demonstrated the potential efficacy of rFVIIa in controlling life threatening PPH.[4-7] In our study, there was reduction in blood loss by 51.4% after administration of factor VII. Similar results were observed in a study by Ahonen et al where rFVIIa administration in severe PPH showed significant reductions in blood loss and cessations of bleeding in 81% of the cases, although it was used as a "last resort" therapy.[12] A 2003 case series by O'Connell et al reported that rFVIIa successfully controlled severe PPH in 13 out of 17 women, leading to the avoidance of hysterectomy in many cases.[13]

Reduction in need for surgical interventions

In a retrospective review by Moscardo et al the use of rFVIIa in 20 PPH patients led to the cessation of bleeding in 14 patients, with only 6 requiring hysterectomies.[14] Similarly in our study out of 41 patients only 15 patients require hysterectomy. It suggests that rFVII could play a role in uterine preservation, which is a crucial outcome for a woman of childbearing age.

Impact on blood transfusions

In our study there was significant reduction in blood product requirement after FVIIa administration. Similar results were found in a study by Searle which showed reduction in volume of blood transfusion by nearly 50% compared to those who do not receive FVIIa.[15] This not only reduced the risk associated with transfusion but also improved patient outcomes.

Safety and thromboembolic side effects

In our study, no adverse thromboembolic events were noted. In a study by Alfirevic et al thromboembolic events occurred in 2% of cases following rFVIIa.[16] These include venous thromboembolism and myocardial infarction. This low incidence concludes that while the use of rFVIIa should be reserved for severe PPH, the benefits often outweigh the risks.

Cost-effectiveness

rFVIIa also reduces costs of therapy and use of blood components in massive PPH. In UK, mean cost of blood components used in a single case is £. 6255, while rFVIIa cost for every patient in treatment is £. 3655.[17] In Italy, a single bolus of rFVIIa 60 µg/kg economically corresponds to cost of 14 PRBC.[18] 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.[12]

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. Small sample size reduces the statistical power and the ability to draw robust conclusions. Patients with PPH with variable causes were included in the study, and the response may differ depending on the underlying etiology.

CONCLUSION

Obstetric haemorrhage can progress rapidly and is strongly associated with the development of disseminated intravascular coagulation (DIC). Delayed correction of DIC is associated with a significant increase in morbidity and mortality. Rapid correction of coagulopathy with ongoing regular monitoring of coagulation status is often difficult to coordinate in the setting of acute life-threatening obstetric haemorrhage. Factor VII helps in haemostasis. The use of blood, FFP, platelets, and cryoprecipitate was reduced in this series in the majority of patients following the administration of rFVIIa, but not in all patients. Where large volume blood loss occurred, adequate red cell replacement may take time to achieve, with patients requiring ongoing transfusion despite an observed decrease in bleeding.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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