Original Article

Use of Recombinant Activated Factor VII: Pakistani Experience of Managing Massive Obstetric Haemorrhage

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Abstract

Background: Massive obstetric haemorrhage is still a prime cause of maternal mortality and morbidity. Remarkable efficacy of off-label use of Recombinant Activated Factor VII (rFVIIa) has been reported in cases of postpartum haemorrhage (PPH) refractory to conventional measures. This study aims to determine the clinical efficacy of rFVIIa for patients with massive obstetric haemorrhage.

Methodology: This was a retrospective cross-sectional comparative study of patients with PPH who received rFVIIa during their treatment at the Department of Obstetrics and Gynaecology from November 2009 to April 2018. The data was collected by chart review on a specified form. The age, parity, cause of bleeding, primary treatment measures followed by rFVIIa treatment were recorded. Time since bleeding to administration of rFVIIa was also recorded. The response of rFVIIa in terms of required transfusion volume, need for ICU/ventilator support, fertility preservation and maternal outcome were also compared and analyzed.

Results: In this study, mean age of patients was 33 ±4 years and uterine atony was the most frequent (>50%) cause of Post-partum Haemorrhage (PPH). Out of 12 patients, 50% received injection rFVIIa who within 6 hours were labelled as early group while 50% received it after 6 hours were labelled as late group. Statistically significant difference was observed in terms of fertility preservation, transfusion requirement and duration of ICU/ hospital stay in early and late groups. Although improved maternal outcome was noted following early rFVIIa administration but it was not found statistically significant between the two groups.

Conclusion: Massive PPH not responding to conventional measures can be managed with early administration of rFVIIa which is an effective haemostatic agent.

Key Message
Massive PPH not responding to conventional measures can be managed with rFVIIa which also has a significant role in preserving fertility if used before hysterectomy.

Introduction

In spite of miraculous advancements in medical science, Postpartum Hemorrhage (PPH) still remains the prime cause of maternal mortality particularly in low-income countries[1]. International Federation of Gynaecology and Obstetrics (FIGO) reported in 2018 that haemorrhage leads to 27% of maternal deaths globally and more than two thirds of them are due to PPH[2] .Classically, PPH is defined as loss of blood volume that exceeds 500mL following vaginal birth and 1000 mL following caesarean[3].Major PPH (more than 1000 ml) can be further divided into moderate

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(1000–2000 ml) or severe (more than 2000 ml[3]. "Definitions of severe PPH vary and include blood loss >1000mL, the need for red cell transfusion or the need for hysterectomy"[4]. Current management strategies for PPH range from initial medical treatments (I/V fluids and pharmacological therapy) to invasive surgical procedures (stepwise devascularization, hemostatic sutures, hysterectomy) and radiological intervention (uterine artery embolization) [5]. Despite this broad range of management options, PPH still remains a leading cause of maternal morbidity and mortality in obstetrics.

Recent advancement have shown remarkable efficacy of "off label" use of recombinant activated factor VII(rFVIIa) in saving lives of women with severe PPH, moreover peripartum hysterectomy can also be avoided in some patients[4,6]. rFVIIa was developed and approved for the treatment of bleeding episodes in patients with haemophilia A, B with inhibitor, Glanzmann's thrombasthenia and factor VII deficiency[7].Other than these indications, any use is considered "off label" and decision to administer rFVIIa depends on the clinician[4].

Haemostasis occurs on two surfaces; cells bearing TF (Tissue factor: a receptor for FVII and FVIIa) and thrombin activated platelets. When an injury occurs, vessel wall is exposed to TF and haemostasis is then initiated at the surface of TF bearing cells which results in generation of thrombin required for activation of platelets. When FVIIa binds TF it activates factor IX and factor X. rFVIIa when administered in adequate doses, directly activates factor X without the need of factor VIII and factor IX ultimately resulting in thrombin burst forming tight plug of fibrin resistant to local fibrinolytic reactions thus making a strong and complex clot[8]. "Since the action of rFVIIa is limited to the site of tissue injury and tissue factor exposure, administration of rFVIIa is considered particularly useful in an obstetric setting where there is often bleeding from a large raw area of exposed tissue"[9].

The remarkable efficacy of rFVIIa has resulted in more than 100 times increase in its use in the management of life threatening bleeding situations ,if compared from last decade, and more than 90% of these are in "off label" indications[8].Very limited data is available on use of rFVIIa in PPH. No randomized controlled studies have been published on PPH[4]. In 2006, an article reviewed internationally published literature reporting rFVIIa use in 65 PPH cases which was found effective[7].A retrospective non randomized study compared 38 patients with PPH who were administered rFVIIa with 26 who were not and a case series of ten patients had also shown good results published in an Indian journal in 2009[4,8]. A large case series and international registries of 272 PPH patients also suggested the effectiveness of the drug[8].Only one local study of three cases had been published in Journal of Pakistan Medical Association in 2005[10].

Despite the evidence of its good haemostatic effect, paucity of data on indications, optimum dosage and complications of rFVIIa has limited its use even in settings where it is affordable[8]. In view of this, we had a good clinical situation to study the efficacy of the drug and share our experience. Thus, we studied the effects of rFVIIa on patients with severe PPH in terms of causes, transfusion requirement, ICU/hospital stay and maternal outcome.

Subjects & Methods

This retrospective cross-sectional comparative study was conducted on patients with massive obstetric haemorrhage at the department of Gynaecology and Obstetrics. The record of 12 patients was reviewed from November 2009 to April 2018 after obtaining approval from institutional ethical committee. These patients with massive obstetric haemorrhage received rFVIIa as a second line therapy when the conventional treatment modalities for PPH had failed. In each case, an informed consent was obtained from husband after counselling regarding off-label use and major possible adverse effects of rFVIIa.

Each medical record was reviewed to assess age, parity, gestational age, labour details, suspected cause of bleeding, management with or without fertility preservation and timing of administration of rFVIIa which was considered early if administered within 6 hours or late if later than that time. Transfusion information pre and post injections were also collected. Need of ventilator support, duration of ICU and hospital stay were noted. Maternal outcome in terms of recovered, morbidity and mortality were also recorded.

All patients received initial treatment of PPH under care of obstetric department including use of uterotonics (intravenous oxytocin, methyl ergometrine, intramyometrialcarboprost and per-rectal misoprostol), local vaginal detailed examination if needed, intrauterine tamponade,

uterine massage and in some cases proceeded to invasive surgical procedures. For prevention and treatment of hypovolemic shock, infusion of crystalloids and transfusion of packed red cells were used. Fresh frozen plasma and platelets concentrate were used for the prevention and treatment of disseminated intravascular coagulation (DIC).

rFVIIa was given intravenously in dose of 90mcg/Kg body weight to those patients in whom conventional medical and surgical treatments were found ineffective. The patients were observed for 20 to 30 minutes for response in terms of patients' vital signs improvement and decrease in amount of bleeding assessed by clinician.

All the obstetric and clinical data thus obtained was analyzed using SPSS version 23. For qualitative variables (age groups, cause of bleeding, timing of injection, ICU stay, maternal outcome etc.) percentages and frequencies were calculated. Using Chi square test, it was determined whether a particular relation found in categorical data (e.g. early/late administration of injection with ICU stay etc.) is statistically significant or not. Likewise, to determine the statistical significance of relation between a qualitative variable (i.e. timing of injection) and a quantitative variable (i.e. transfusion requirement and hospital stay), their means were compared using Student T-test. Relations were considered statistically significant if p value<0.05.

Results

The detailed obstetric and clinical data of each patient is given in Table 1.A total of 12 cases of severe PPH were included in this study. Mean age of patients was 33 ±4 years. Mean gestational age was found to be 36±2 weeks. Median parity of patients was 2±1. About 83% (n=10) of patients delivered via Caesarean section and 16% (n=2) delivered vaginally. In this study, uterine atony was the leading cause of PPH along with abnormal placentation (placenta praevia and morbidly adherent placenta) and the rest of the causes included retained products of conceptus, placental abruption and birth canal tears. Figure 1 shows the the proportion of patients with preserved fertility while figure 2 shows frequency of various maternal outcomes.

While compiling the data of 12 patients it was found that they can be categorized and compared as two groups i.e. early group who received rFVIIa within 6 hours of haemorrhage and late group who received rFVIIa after 6 hours of haemorrhage. The comparison of two groups was made in terms of ICU/hospital stay, mean transfusion requirement, uterine status and maternal outcome (Table 2).In early group, fertility preservation was observed in all patients along with lesser ICU/hospital stay and mean transfusion requirement and this difference was statistically significant. Moreover, there was better maternal outcome following early administration of rFVIIa but this difference was not found statistically significant.

Table 1: Obstetric and Clinical Data of Patients Receiving rFVIIA

Case	1	2	3	4	5	6	7	8	9	10	11	12
Age(Years)	36	36	35	31	29	25	36	37	34	37	35	25
Parity	1	2	2^{+2}	3	1	PG	4	2	2	5^{+1}	5^{+2}	1
Gestational age(weeks)	37	36	35^{+6}	38	39^{+2}	39	37	33	35	32	37	37
Mode of delivery Vaginal delivery (VD) Caesarean delivery (CD)	CD	CD	CD	CD	VD	CD	CD	CD	CD	CD	CD	VD
Causes of bleed Atony	+	+	+	+	+	+	+	+	+	+	+	
Abnormal placentation	+	+					+	+	+			
Abruption			+									
Cervical tear												+
Retained placenta/ fragments											+	
Pre-eclampsia			+	+								
Interventions prior to rFVIIa Uterotonics	+	+	+	+	+	+	+	+	+	+	+	+
Haemostatic suture	+		+				+	+	+	+		
Uterine devascularization	+					+				+		
ERPC				+	+	+					+	+
Tamponade				+	+	+	+	+			+	+
Hysterectomy	+	+	+					+	+			
Cervical tear repair												+
No. of Transfusions Prior to rFVIIa RCC	18	3	4	5	3	5	4	7	6	2	3	2
FFPs	22	6	10	8	4	8	7	12	10	4	4	4
Platelets	11	2	6	4	0	3	2	2	6	1	1	0
After rFVIIa RCC	3	2	2	0	1	1	1	1	1	0	0	0
Timing since Haemorrhage to rFVIIa (Hours)	10	8	7	5	4	6.5	3	7	7	2	4	2
ICU stay(Days)	10	2	2	0	0	0	0	1	0	0	0	0
Hospital Stay(Days)	10	8	15	8	3	7	7	7	15	10	3	3
Uterine status Saved (S) Hysterectomy (H)	H	H	H	H	S	S	S	S	H	H	S	S
Maternal outcome Alive with no significant morbidity (A) Alive with significant morbidity(AM) Dead(D)	D	A	AM	AM	A	A	A	A	A	A	A	A

Table 2: Relation of Time of Injection with Various Maternal Parameters

Parameters	Early Group (n=6)	Late Group (n=6)	P-Value
Mean ICU Stay(days)	0	2.5±3	0.04
Mean Transfusion Requirement (n)	10±4	25±14	0.03
Fertility preservation(n)	6/6	1/6	0.03
Mean Hospital Stay(days)	5±3	10±3.7	0.01
Maternal Outcome (%)			
(i) Alive without significant morbidity	83%	66.6%	0.5
(ii) Alive with significant morbidity	17%	16.6%	
(iii) Dead	0%	16.6%	

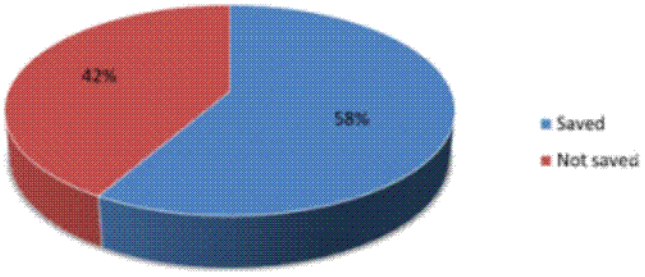

Figure 1: Uterine status of Patients

Figure 2: Frequency of Various Maternal Outcomes

Discussion

Primary post-partum haemorrhage (PPH) is a potentially life threatening complication and is one of the most difficult challenges for obstetricians. A review by M Franchini et al confirms that patients with age more than 30 years are at risk of developing PPH and uterine atony was found to be the most common cause[7].In present study, 75% patients were of more than 30 years age and the major cause of bleeding was uterine atony (Table 1). AII patients of PPH in this study were managed through conventional methods including volume, RCC (Red Cell Concentrate) and clotting factors replacement. The rFVIIa was only used after failure of above treatments and clotting factor replacement. A review by American group suggested that use of rFVIIa is only suitable in the management of PPH when replacement of clotting factors had failed to arrest the haemorrhage[11].The overall requirement of red blood cells and fresh frozen plasma was also decreased following administration of rFVIIa. Same observation is reported by Soon Chang et al in his study, thus highlighting that the magnitude of severe PPH can be diminished by rFVIIa[12].

No proper guidelines for rFVIIa dosage in PPH were available for a long time so a variable dose(15 to 120mcg/Kg) of rFVIIa were being used by clinicians[13]. In 2008, guideline by Welsh A et al recommended "90mcg/Kg body weight of rFVIIa as a single bolus injection over three to five minutes"[4]. The single dose of 90mcg/Kg body weight was used in the present study and was found effective. Ogawa et al observed the same results in their study[13]. Welsh A et al also recommended repeat dose after 20 minutes if there is no response and significant bleeding is continued[4]. The indicators to assess the effect of rFVIIa include "visual evidence, stabilization of hemodynamic parameters and reduced demand for blood components"[14].

In the present study, this injection was used initially as a last resort to save life. Fertility could not be preserved in approximately 83% of cases (late group), however when the injection was administered earlier, fertility was preserved in 100% of cases. Ahonen & Jokela also shared same experience**.** In their study, 5 out of 12 cases underwent hysterectomy before rFVIIa injection was administered. However afterwards rFVIIa was found effective in avoiding hysterectomy[15]. A review article in 2016 also stated that in uncontrolled PPH, rFVIIa should be used before surgery if there is no placental pathology indicative of hysterectomy[16].

Magon et al suggested that "rFVIIa should be considered earlier in management before patient's condition worsens and she starts slipping out of hands"[16]**.** This finding was observed in our study too. Magon further emphasized the earlier use of rFVIIa especially in low resource health care systems as in India, where trained birth attendants handle major bulk of deliveries who do not have surgical skill for haemostatic suture and there may be non-availability of operation theatre facility. This is also applicable in our setting as we share the same socioeconomic dynamics.

The use of rFVIIa carries the risk of thromboembolic events because it is an activated factor and its administration in pharmacological doses results in an increase of rFVIIa by 1000 times[17]. However Aledort LM quoted that the occurrence of such complications after rFVIIa administration is very rare[18]. Recombinant activated factor VII (rFVIIa) used in a PPH patient even with DIC but no previous co-morbidities also has low thromboembolic risk[10]. It should be used with care in patients with pre-existing risk factors such as obesity and diabetes mellitus[10]. In this study, no such complications were encountered. In a study of 15 cases of PPH managed with rFVIIa, no such complication was observed even in the presence of relatively hypercoagulable state pregnancy[19]. Similarly, Soon Chang et al also encountered no complication in patients who received rFVIIa[12].

High cost of this injection is a limiting factor in its use. However, timely use of rFVIIa reduces the cost of therapy and also use of blood components in massive obstetric haemorrhage. In this study, reduced requirement of blood products was noted when rFVIIa injection was administered earlier and this difference was statistically significant ($p<0.05$). Similar findings were observed by SH Moon et al[20].Moreover, statistically significant difference was also observed in ICU stay and hospital stay of patients in these two groups($p<0.05$). The patients with early administration had reduced number of ICU procedures and hospital stay. Only 4 patients out of 12 required ICU care and 2 patients with morbidity (acute renal failure/infected wound) had prolonged hospital stay, rest of the patients were discharged within 15days (mean 8±4 days). Use of rFVIIa in uncontrolled PPH can be economical as it reduces requirement of blood products transfusions and minimizing complications requiring ICU management. This statement is supported by studies done in the nations where cost-effectiveness of resources matters. "In UK, mean cost of blood components used in a single case is £ 6255 while rFVIIa cost for every patient in treatment is £ 3655"[21]. Ahonen et al also stated that one rFVIIa injection equals the cost of "transfusion with 50 units of red blood cells or an embolization procedure or ICU treatment of 2 days"[15].

This study shows promising results of off-label use of rFVIIa in the management of massive obstetric haemorrhage.

There are some limitations of our study that should be acknowledged.

The review of cases was done retrospectively; As all patients in the study received rFVIIa with no control group, interpretation has limitations; Evaluation of efficacy of rFVIIa has limitations as many other therapeutic measures have also been done in all the patients.

Conclusion

Massive PPH not responding to primary conventional measures can be managed with rFVIIa which is an effective haemostatic agent and has a significant role in preserving fertility if used before hysterectomy. Early administration of this injection improves the outcome significantly.

Only Randomized controlled trials (RCT) is an optimal way to define the true role of rFVIIa in massive PPH, but such trials will not be ethical to perform because of life threatening nature of PPH. Thus, results from other studies like present study can contribute in evolution of guidelines for rFVIIa use in massive obstetric haemorrhage.

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