Recombinant activated factor VII in post partum haemorrhage

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INTRODUCTION

Post-partum haemorrhage (PPH) is a life-threatening obstetric complication, which mainly occurs without any warning, predictive signs or symptoms and often in the absence of predisposing conditions. It is the most commonly reported complication and the leading cause of maternal death, and there is no controversy about the need for prevention and treatment of PPH. Recent evidence from the World Health Organization (WHO) strongly suggested that deaths due to PPH were underestimated and could reach as high as 40% of all maternal mortality in some African countries as well as Southeast Asia and Latin America. 3

Unlike uterine rupture that can precede death by 24 h and antepartum haemorrhage, which may lead to death in half that time, PPH can be lethal in as little as an hour. The risk of dying from PPH depends not only on the amount and rate of blood loss but also on the health status of the woman who is bleeding. 2 Conventionally, blood loss after delivery is visually estimated with wide variations in accuracy. Williams emphasized the importance of accurately measuring vaginal blood loss at delivery as early as 1919. 4 The birth attendant grossly makes a quantitative estimate; however, the associated amount of loss is often far greater than appreciated by visual estimation alone. 4 Published studies, in which investigators carefully quantified blood loss after delivery, repeatedly indicate that clinical estimates of blood loss are notoriously unreliable, with a tendency to underestimate the incidence of PPH by 30-50%. Often, this results in delay assessing of the gravity of situation and therefore in delaying decision-making, which in turn delays instituting resuscitative measures and, at times, irreversible delays lead to maternal mortality. 3

One issue that causes delays is reaching a threshold to act, which is complicated by the issue of how to define and quantify PPH. An extensively used definition is ‘any blood loss from the genital tract during delivery above 500 ml,’ as proposed by WHO. 5 However, around 5% of women lose >1000 ml during a vaginal birth. Caesarean deliveries are associated with an average estimated blood loss of 1000 ml. There is, therefore, a degree of overlap in the acceptable range of blood loss for vaginal and caesarean deliveries. WHO recently examined studies on PPH published between

ABSTRACT

Post-partum haemorrhage (PPH) is a life-threatening obstetric complication and the leading cause of maternal death. Any bleeding that results in or could result in haemodynamic instability, if untreated, must be considered as PPH. There is no controversy about the need for prevention and treatment of PPH. The keystone of management of PPH entails first, non-invasive and nonsurgical methods and then invasive and surgical methods. However, mortality remains high. Therefore, new advancements in the treatment are most crucial. One such advancement has been the use of recombinant activated factor VII (rFVIIa) in PPH. First used 12 years back in PPH, this universal haemostatic agent has been effectively used in controlling PPH. The best available indicator of rFVIIa efficacy is the arrest of haemorrhage, which is judged by visual evidence and haemodynamic stabilization. It also reduces costs of therapy and the use of blood components in massive PPH. In cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before surgery. We share our experience in a series of cases of PPH, successfully managed using rFVIIa.

Key words: Haemostasis, maternal mortality, novoseven, post-partum haemorrhage, recombinant factor-VIIa

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1997 and 2002 to arrive at more precise definitions of PPH and its incidence. It was astonishing, but true that data from 50 countries, 116 studies and 155 unique data sets was reported to be of poor quality. Indeed, one of the major problems plaguing the research is how to measure PPH accurately. As discussed above, clinical visual estimation of blood loss is not reliable. Interestingly, in Tanzania, the use of Kangas has been adopted as a valid instrument tool. Pre-cut Kangas is a standard-sized rectangle of 100 cm × 155 cm made of local cotton fabric. When 3-4 Kangas are soaked at a delivery, the trained birth attendant (TBA) is entrusted to transfer patients to a health centre. Similarly, all centres caring for women have to evolve their standards, and thresholds need be set for initiating different steps in the management of PPH. Indeed, any bleeding that results in or even perceived could result in haemodynamic instability, if untreated, must be treated energetically as PPH.

The keystone of management of PPH entails first non-invasive and nonsurgical methods and then invasive and surgical methods. Prompt management with effectual fluid and blood transfusion and with uterotonics drugs is the first-line therapy. If these are unable to control bleeding, more drastic and invasive interventions such as uterine compression sutures, systemic pelvic devascularization, angiography with selective embolization, or finally, as a last resort, hysterectomy can be performed. However, mortality and morbidity related to PPH continues to remain unacceptably high even in developed countries, contributing to hysterectomy in at least 50% of cases. Moreover, only a few centres worldwide have access to the aforesaid procedures. Early, effective and preferably non-invasive treatments that can reduce maternal mortality and morbidity from PPH and save future reproductive potential of the woman are therefore essential.

One of the recent and novel advancements in the management of PPH has been the use of recombinant activated factor VII (rFVIIa) (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark). It was initially developed for the treatment of bleeding episodes in patients with haemophilia A or B. Beyond its currently recognized indications, rFVIIa has been effectively used ‘off label’ on an empirical basis in the treatment of massive PPH. From the first reported usage of rFVIIa in obstetric haemorrhage almost a decade back, it has made an impressive journey and saved many human lives. In last decade, there have been a number of case reports and series documenting successful management of PPH using rFVIIa. There are no randomized controlled trials conducted, and for reasons that hardly require amplification, it is highly implausible that they will ever be performed in patients with life-threatening PPH. Our experiences in a series of five cases, two of atonic, one of traumatic and two with mixed PPH that were successfully managed using rFVIIa has been shared first, followed by a discussion on the scope of rFVIIa in obstetric haemorrhage.

**OUR EXPERIENCE**

The first case was a primigravida, who underwent an emergency caesarean delivery for arrest of descent at full dilatation. Intra-operatively, the placenta was found adherent, which was removed manually. After placentation, uterus was astatic despite giving uterotonics sequentially in adequately repeated doses of oxytocin, ergometrine and carboprost tromethamine (15-methyl derivative of prostaglandin F2α). Uterine compression sutures were applied and bilateral uterine and ovarian vessel ligation was performed. The bleeding was arrested and the abdomen was closed. Total blood loss by this time was around 2 l and adequate volume replacement was done with intravenous crystalloids and 2 packs of whole blood. Oxytocin infusion was continued. As soon as the patient was to be shifted out of operating theatre, she re-started bleeding profusely per vaginum. Abdomen was reopened and a clinical decision to perform hysterectomy was taken and a subtotal hysterectomy performed. Bleeding decreased, but continued. Total blood loss was estimated to be around 3.5 l by this time. At this stage, we decided to give rFVIIa. Inj TFVIIa (NovoSeven®; Novo Nordisk A/S, Bagsvaerd, Denmark) 60 µg/kg body weight of patient was given intravenously. By subjective evaluation, bleeding decreased significantly. Abdomen was closed. Another dose of 60 µg/kg was repeated after 30 min of initial dose. Bleeding stopped after 10 min of the second dose. Another 3 packs of packed cells were transfused later.

The second patient was a primigravida who underwent a vaginal delivery at the hands of a midwife and had a PPH. She was brought under obstetrician’s care almost 40 min post-delivery. On examination, the uterus was well-contracted and she had a cervical tear and multiple vaginal lacerations, which were all actively bleeding. Cervical tear was sutured. Vaginal mucosa had become edematous and endeavours to perform haemostatic suturing there caused cutting through of sutures and more trauma. Total blood loss was estimated to be almost 2.5 l by this time. Volume replacement was simultaneously and effectively done with crystalloids and 3 packs of whole blood. Inj Tranexamic acid (1 gm) was given intravenously, which could not arrest bleeding. Tight vaginal packing was done, which got soaked with blood in no time and blood was oozing out from the pack. At this juncture, the decision to use rFVIIa was taken. We gave Inj rFVIIa at 60 µg/kg body weight. Bleeding decreased and was completely arrested within 30 min. Third case was again of a primigravida who had an elective caesarean delivery for breech presentation. After delivery of placenta, she had atonic PPH. Despite all uterotonics, bleeding continued. Uterine compression sutures were applied and bilateral

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*Note: The above text is a continuation of the previous document and provides additional context and details.*
uterine and ovarian arteries were ligated. Total blood loss was around 2 l by this time. Bleeding continued. Effective volume replacement was simultaneously done with crystalloids and whole blood. At this juncture, an obstetric hysterectomy was contemplated. However, this time, we decided to use rFVIIa first and to go ahead with hysterectomy as a last resort, in case bleeding was not arrested. rFVIIa was used at 60 µg/kg body weight was given, and, within 30 min, the bleeding was arrested.

Fourth case was of a diabetic primigravida who underwent a vaginal delivery at home and was brought to us with PPH almost 1 h post-delivery. She had a combination of both anatomic and traumatic PPH. Despite all conservative methods and the use of all possible uterotonics, the uterus was becoming atonic repeatedly. Also, she had multiple vaginal lacerations, which were bleeding and not amenable to haemostatic suturing. She had a blood loss of almost 1 l after coming to the hospital and an estimated same amount before coming. Although volume replacement with crystalloids and whole blood kept her haemodynamics stable, her bleeding could not be controlled. We had an option of laparotomy and trying surgical techniques of uterine compression sutures, systemic devascularization or obstetric hysterectomy, but the patient and her spouse wanted to preserve fertility. As uterotonics and bimanual compression were not successful in arresting haemorrhage, we realised that the chances of controlling haemorrhage with uterine devascularization and suturing were limited. Also, the actively bleeding vaginal lacerations were another cause of concern. After discussion with patient’s spouse, we decided to use rFVIIa and prepared to go ahead with laparotomy and proceeded in case bleeding did not get arrested with the same. Oxytocin drip was continued and uterine message was also continued. Within 20 min of giving rFVIIa, uterus regained its tone, and bleeding from vaginal tears was significantly reduced. Vaginal packing was done and bleeding got completely arrested. Pack was removed after 24 h. The patient had uneventful hospital stay after that. Our fifth case was of a second gravida, a post caesarean pregnancy with a special first child, who underwent an elective caesarean. Intra-operatively, there were two big subserosal fibroids. The patient had a post-delivery atony and bleeding from one of the fibroids as well, which was accidentally injured during extraction of baby. Despite all uterotonic drugs and conservative surgical techniques, she was bleeding profusely. rFVIIa was used at 90 µg/kg and effective volume replacement was done. Bleeding got arrested within 20 min.

Before giving rFVIIa, we ensured a pH >7.2, platelet counts >50,000/mm³ and fibrinogen levels >150 mg/dl in all our patients. 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).

Lessons learnt
Five cases of PPH in which rFVIIa was used for management have been discussed. In the first case, it was used post-hysterectomy and as a last resort. In the second case, it was used to arrest haemorrhage from multiple vaginal lacerations, which were not amenable to haemostatic suturing. This happens many times when there are multiple vaginal lacerations and especially some time has elapsed after delivery and vaginal mucosa becomes fragile and edematous. In such cases, it becomes very difficult or at times even impossible to arrest haemorrhage. In massive PPH, coagulopathic factor adds to the surgical bleeding. Bleeding from larger vessels may be controlled by using various surgical methods, however the ability to control diffuse bleeding is limited and, often, not feasible. Consequently, haemostatic drugs that can control the coagulopathic component of blood loss may reduce mortality and morbidity in such patients. rFVIIa appears to be effective in such cases, both as a adjunctive to surgical haemostasis as well as a rescue therapy, where PPH is refractory to current pharmaceutical and ‘uterus sparing’ surgical techniques. In the third case, we used rFVIIa prior to performing obstetric hysterectomy. Bleeding was arrested and an almost foreseeable hysterectomy was prevented. In the fourth case, a relatively early decision to use rFVIIa helped prevent a laparotomy and a possible hysterectomy. Because of its mechanism of action, rFVIIa has a potential to function as a universal haemostatic agent across a range of indications. In the last case, it seemed to prevent a hysterectomy, which almost looked inescapable. Our experience coupled with the worldwide data suggests that last 10 years of its journey in controlling PPH have been indicative for efficacy and safety of rFVIIa in the maternal population. rFVIIa is presently being used as initial therapy as well as a life- and uterus-saving therapy in life-threatening PPH.

OVERVIEW OF HAEMOSTASIS & ROLE OF rFVIIa
Physiologically, coagulation occurs in 3 overlapping phases: Initiation, amplification and propagation. Tissue factor (TF) is a membrane-bound glycoprotein, expressed on subendothelial cells and is exposed only when endothelial cell barrier is disrupted following injury. As soon as vessel wall is injured, TF is exposed and serves as a high-affinity receptor to circulating FVIIa, leading to the formation of a TF — VIIa complex, which initiates coagulation. TF is a co-factor to FVIIa. FVIIa attains its full proteolytic activity once complexed to TF. TF — VIIa complex activates factor IX and factor X on the surface of TF-bearing cells, and factor Xa binds to factor Va on the cell surface. The factors Xa — Va complex initiates conversion of small amounts of prothrombin to thrombin at the surface of subendothelial cells. This small amount of thrombin is
not sufficient for fibrinogen cleavage, but is critical for haemostasis, as it can activate platelets. In amplification, this small amount of thrombin activates factors V and VIII and platelets. The activated platelets bind factors Va, VIIIa and IXa. Factor VIIIa — IXa complex activates factor X on the surface of activated platelets. Platelet-surface factor Xa is relatively protected from normal plasma inhibitors and can complex with platelet-surface factor Va, where it activates thrombin in quantities sufficient for fibrinogen cleavage. During propagation, the factor Xa — Va complex activates large amounts of prothrombin, resulting in a ‘thrombin burst,’ which converts fibrinogen to fibrin and activates fibrin-stabilising factor XIII. It is the amount and rate of thrombin generation that determines the strength of the haemostatic plug.

rFVIIa promotes haemostasis locally at the site of vascular injury, where TF is expressed and activated platelets are found. Its acts in two ways: A TF-dependent pathway and TF-independent pathway. Pharmacological concentrations of FVIIa overcome the inhibitory effect of zymogen FVII on FVIIa — TF initiated thrombin generation, and this too contributes to its therapeutic effect. However, if TF is not available or TF pathway inhibitor inhibits its activity, then rFVIIa-mediated large-scale thrombin generation takes place on the activated platelet surface independently of TF. At pharmacological concentrations, rFVIIa directly activates factor X on the surface of locally activated platelets, helping generate thrombin and fibrin (platelet-dependent TF-independent pathway). This results in the conversion of prothrombin into large amounts of thrombin. The full thrombin burst mediated by factor Xa in complex with factor Va is necessary for the formation of a fully stabilized and solid fibrin haemostatic plug. Uncontrolled thrombin generation and fibrin deposition have not been observed in experimental settings following systemic administration of rFVIIa.

Pharmacokinetic evaluations suggest that the elimination of rFVIIa follows linear kinetics with a faster clearance rate and shorter half-life when rFVIIa is administered for bleeding episodes as compared to non-bleeding indications. Therefore, the duration of action may be shorter when rFVIIa is used to control bleeding episodes. An increased elimination rate and lower recovery of rFVIIa during bleeding may be related to consumption through complex formation with TF exposed at the site of vessel damage and on the phospholipids exposed on the activated platelet surface.

The best available indicator of rFVIIa efficacy is the arrest of haemorrhage judged by visual evidence, hemodynamic stabilization and reduced demand for blood components. There is currently no satisfactory laboratory test to monitor the clinical effectiveness of rFVIIa, which is judged subjectively. Administration of rFVIIa results in shortening of the prothrombin time (PT) and the activated partial thromboplastin time (APTT). It does not do so in factor V- or factor X-deficient plasma and is therefore not beneficial in patients completely deficient in these factors. The APTT shortening is due to the direct activation of factor X by circulating FVIIa on the phospholipids used in the PTT test. However, shortening of these two screening tests of coagulation does not necessarily reflect clinical effectiveness, which is judged subjectively. Clotting parameters obtained prior to rFVIIa administration are often outside the normal range, perhaps indicating the development of dilution or consumption coagulopathy in these patients. Post rFVIIa, clotting parameters improve, but do not normalize, and thus cannot be used as predictors of rFVIIa efficacy.

rFVIIa is associated with very few adverse events and is well tolerated. Data accumulated from its global usage for various indications has brought that the incidence of non-serious adverse events is 13% and serious adverse events are <1%. Risk of rFVIIa related thrombosis is 25 per lakh infusions. Non-serious side effects include pain at the infusion site, fever, headache, vomiting, changes in the blood pressure and skin-related hypersensitivity reactions.

rFVIIa is a recombinant product, and its availability is not affected by scarcity of blood. It does not carry risk of viral transmission because it is free of any human protein. It causes localized haemostasis and has low thrombogenicity. In studies where rFVIIa has been added to factor VIII- and IX-deficient plasma, there has been no enhancement of free thrombin generation, indicating that rFVIIa does not induce a hypercoagulable state. It has a low risk of anaphylaxis and has no anamnestic responses. However, its short half-life and frequent repetitive dosing are few of its limitations. As with most of other drugs in the world, it is also not 100% effective. It has no measurable lab 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.

rFVIIa is perceived as an expensive drug, which it is indeed. However, from various studies conducted in western nations where laborious cost calculations are done, rFVIIa has been reported to reduce costs of therapy and use of blood components in massive PPH. In Italy, a single bolus of rFVIIa at 60 μg/kg equals to the cost of 14 PRBC. In UK, blood components worth £6255 are used in a single case, whereas rFVIIa cost for a patient in treatment is £3655. In Finland, the cost of a single rFVIIa dose is similar to that of transfusion with 50 units of RBC or an embolization procedure or a 2-day intensive care unit (ICU) stay. Also, we must remember that there is no cost of a human life! Clinicians caring for acutely bleeding obstetric patients should be aware of the potential of rFVIIa to arrest life-threatening PPH. Although an expensive product, a trial of one to four doses of rFVIIa can be justified in cases of uncontrolled bleeding, which persists despite maximal
possible medical and surgical treatments to achieve haemostasis.

Currently, rFVIIa is available as a room temperature-stable product in 1 mg and 2 mg strengths. rFVIIa can be given by slow intravenous injection in a dose of 60-90 µg/kg body weight and can be repeated after 20-30 min, based on clinical response. According to Australia New Zealand guidelines, rFVIIa dosage of 90 µg/kg (up to 2 doses) is advocated for refractory PPH not responding to conventional approaches; only after failure to trial of rFVIIa therapy, hysterectomy is considered.

Before administering rFVIIa, minimum fibrinogen levels of 100 mg/dl, (preferable >150 mg/dl), international normalized ratio <1.5 and platelet counts >50,000/m³ should be ensured. Haemoglobin levels should be preferably >7 g/dl. In case of any derangements of these parameters, they must be corrected by using appropriate therapy before rFVIIa is used. Patient should not be in metabolic acidosis and pH should be ≥7.2, otherwise efficacies of rFVIIa decrease. Although rFVIIa retains its activity in the presence of hypothermia, if possible, body temperature should be maintained within physiological values. It is recommended that the decision to use rFVIIa should be taken in time during management of PPH before metabolic complications develop and before the symptoms of severe thrombocytopenias, hypoxia and organ injury appear.

CONCLUSION

We believe that, in cases of intractable PPH with no other obvious indications for hysterectomy, administration of rFVIIa should be considered before hysterectomy. We recommend administration of rFVIIa early in the course of management in few special situations like when no blood is available and in patients with acquired haemophilia. rFVIIa should be considered in the management of PPH before packing of the uterus or pelvis and before considering surgical procedures like peri-partum hysterectomy or laparotomy in cases of vaginal delivery. In cases with actively bleeding multiple vaginal lacerations, especially in patients brought to an obstetrician’s care some time after delivery, with edematous vaginal mucosa not amenable to haemostasis with suturing, rFVIIa should again be considered early in the management before patient’s condition worsens. Indeed, in India, and many other developing nations, where a relatively major percentage of deliveries are handled by TBA and midwives and at centres where the available manpower resources may not have expertise in haemostatic suturing techniques, it is important that rFVIIa must be made available. All public and private agencies that have stakes in women’s health must join hands together to make this drug available at such centres for usage in life-threatening PPH. In patients who do not accept blood or component transfusions (e.g., Jehovah Witnesses), rFVIIa is one of the very few life- and uterus-saving treatment available.

Maternal mortality is an important statistical measure for assessing a nation’s health. Achievement of Millennium Development Goal 5 (MDG-5), which aims to reduce maternal mortality by three-quarters, seems to be a daunting task for most developing countries. Physicians who deliver healthcare to women are also desperate to reduce maternal mortality, however not by three-quarters, instead to zero. As was famously said once by Mamoud Fathulla, past FIGO president that for the physicians who serve the health needs of women, maternal mortality is not mere statistics. It is not numbers, neither rates nor ratios. Maternal mortality is about women. It is women with names and faces, women who had come with hopes and women whose faces reflect the throes of their agony, distress and despair. This is not only because these are women die in the prime of their lives, at a time of great expectation and joy, but also because, in almost each and every case, in retrospect, it is an event that could have been prevented. It is an event that bears and should bear so heavily on our collective conscience, enough to shake human soul and to leave an ever-lasting impact. PPH is the biggest such scourge responsible for shaking souls.

We need to prevent PPH in the first place, and, in case it happens, to aggressively manage it with all available resources in our armamentarium. Aim of the management should be to save every drop of blood, because with every additional drop of blood lost, the condition of the patient worsens and the patient enters a vicious cycle of haemorrhage, coagulopathy and hypothermia. Often, the patients are lost because too little is done too late. The review of the data available worldwide and our own experience shows that rFVIIa is an effective haemostatic agent. It is important that further studies be done and experiences shared worldwide on this seemingly effective drug, which has done an impressive journey in the last one dozen years and has the potential to help achieve MDG-5. This is the duodecennial of rFVIIa in helping mothers survive.

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