Case Series

Use of Recombinant Factor VIIa for Massive Postpartum Haemhorrage: Case Series and Review of Literature

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Abstract

Recombinant activated factor VII is indicated mainly for the treatment of patients with haemophilia inhibitors. It has also been found successful in the treatment of platelet disorder Glanzmann's thrombasthenia. Recently, its use in trauma patients and in patients with intracereberal haemorrhage has become well established. We present three cases of massive post partum haemorrhage treated with rFVIIa, following caesarean section. The response of these three patients is discussed along with review of literature.

Introduction

Postpartum haemorrhage is the major cause of maternal mortality in both developed and developing countries. In the developing world, the risk of maternal death from postpartum haemorrhage is approximately 1 in 1000 deliveries.[1] There are approved guidelines and protocols for the management of postpartum haemorrhage. These include both medical and surgical measures to control blood loss. There are a number of case reports where empirical off label use of recombinant factor VIIa (rFVIIa NovoSeven, Novo Nordisk, Denmark) has been effective in the treatment of massive postpartum haemorrhage which did not respond to conventional methods.[2]

Factor VIIa acts via tissue factor pathway. It circulates in minute quantities and binds to tissue factor (TF) expressed on the damaged vascular bed. This TF-FVIIa complex activates FIX and FX on TF bearing cells. FXa activates FV; this FXa-FVa complex on TF bearing cells rapidly converts small amounts of prothrombin into thrombin. Thrombin then activates platelets, FVIII, FV and FXI. On the surface of activated platelets, FVIIIa and FIXa gather to activate large quantities of FX which eventually result in large thrombin burst enabling the conversion of fibrinogen into fibrin with initial clot formation. The exogenous administration of rFVIIa accelerates the above process and helps in securing haemostasis by clot formation.[3]

In vitro studies have shown that compared with normal clot, the fibrin clots formed in the presence of high thrombin concentration generated by rFVIIa have a different architecture; is stronger and is more resistant to degradation by fibrinolytic enzymes.[2]

We present a series of three cases of uncontrolled massive PPH where it was used as a last resort to control bleeding. A brief literature review is also presented.

Case 1

A 27 years old primigravida was referred to a tertiary referral centre for foetal distress due to chorioamnionitis. An emergency caesarean section was done. Outcome was an alive healthy female with good apgar score. She was discharged from the hospital after her routine post-operative stay of five days. The patient was readmitted 48 hours later in a collapsed state. Initial supportive measures included transfusion of six units of whole blood, and five units of fresh frozen plasma. Her pelvic ultrasound revealed huge collection and dehiscence of uterine scar. Emergency laparotomy under general anaesthesia was done with repair of the uterus and insertion of peritoneal drains. The woman continued to bleed and 12 hours later underwent another laparotomy for removal of uterus. Third laparotomy was done for bilateral internal iliac ligation. By this time, she was transfused seventeen units of fresh frozen plasma, two doses of single donor platelet transfusion and thirteen units of whole blood. She required inotropic support to maintain haemodynamic status. Her haemoglobin by this time had dropped to 5.3 gm/dl, platelets 66000, prothrombin time 18 seconds versus 13 seconds and activated partial thromboplastin time (APTT) 38 seconds versus 35 seconds, D dimmer 0.38 FEU. Her drains kept on filling at a rate of 225ml/hour along with bleeding per vaginum. At this time haematology advice was obtained; it was decided to give rFVIIa because all the conventional measures to control bleeding had failed. rFVIIa dose was calculated as 90 ug/kg; total dose was 450 ug (body weight 51 kg). Haemostasis was secured within 16 minutes. There was no blood loss from any drain or per vaginum. Her blood picture twenty-four hours later showed haemoglobin 6.5 gm/dl, platelets of 30000, prothrombin time 13 versus 11 seconds and APTT 35 versus 33 seconds. Two units of top-up packed red cells and two units of fresh frozen plasma were transfused in next 24 hours. Her bleeding per vaginum stopped, she stayed in intensive care for another 72 hours and then was shifted back to the ward for routine post-operative care. No thrombo-embolic episode was noted during follow up period.

Case 2

A 35 years old woman para five and gravida 6 with history of previous Caesarean section was admitted in the antenatal ward. At presentation, she was 26 weeks pregnant and complained of loss of foetal movements. Investigations at the time of admission showed haemoglobin of 6 gm/dl,

while pelvic ultrasound reported an intrauterine dead foetus. Her placenta was anteriorly sited. She received three units of whole blood for correction of anaemia. She went into spontaneous labour and delivered a dead baby of one kg; placenta was retained. She was shifted to theatre for manual removal of placenta under general anaesthesia. Sub total hysterectomy was carried out after failure to remove it manually; placenta was found to be adherent, placenta percreta along with dehiscence of uterine scar. During the procedure, she required eight units of whole blood and seven units of fresh frozen plasma. Her haemoglobin dropped to 6.5 gm/dl, platelets 33000/cmm, PT was 17 seconds over a control of 12 seconds and APTT 36 with a control of 33 seconds. Her peritoneal drains collected with 600 cc of blood within 40 minutes of laparotomy. Because of haemostatic failure, clinical haematologist was asked to help; on his advise rFVIIa was given to rescue from massive uncontrolled blood loss at a dose of 90 ug/kg; total dose 360 ug (body weight 45 kg). She required two units of top-up transfusion of packed red cells and two more units of fresh frozen plasma. Blood loss stopped completely in 14 minutes in the drain and bleeding per vaginum stopped after two hours she was discharged from intensive care after 48 hours of stay, for routine post operative care in ward. No thromboembolic episode was noted during the follow up period.

Case 3

A 30 years old lady, para 0+1, was a known case of systemic lupus erythematosis (SLE) with renal involvement. She was booked in the antenatal clinic for antenatal care. Her antenatal period was eventful as she required intensive follow up with nephrologists, and haematologist. Throughout her antenatal period she was on steroid therapy, low molecular weight heparin, aspirin along with anti anaemics. At 34 weeks of pregnancy, she had preterm pre labour rupture of membranes. Emergency caesarean section was done under spinal anaesthesia. Her surgery was uneventful, no transfusion was required. A live baby boy 3 kg with good apgar score was delivered.

Twenty-four hours later, abdominal distension along with drop in Haemoglobin from 10 gm/dl to 5 gm/dl was noted. Platelets dropped from 284,000 to 59000. Her prothrombin time was 17seconds with a control of 12 seconds and D dimmer rose to >8 FEU. Emergency laparotomy was carried out. Per operatively, a large muscle haematoma was noted. Peritoneal cavity also showed collection of 500 cc of blood, along with generalized oozing from stitch line. Few reinforcing stitches were applied along with insertion of peritoneal and Redivec drains. Both the drains again showed collection of 150 cc during shifting of patient to intensive care. After getting haematologists' opinion, it was decided to give rFVIIa, in a dose of 80 ug/kg; total dose 4.8 mg (body weight 65 kg) as a general haemostatic agent to stop further bleeding, as the patient had a multi system autoimmune disorder. She required four units top-up packed cells transfusions and two units of fresh frozen plasma. Her peritoneal and Redivec drains did not show further accumulation of blood. She was discharged from intensive care after 48 hours.

Discussion

Recombinant factor VIIa is licensed for use in the treatment of haemorrhagic episodes in haemophilic patients with inhibitors to factor VIII and IX, congenital factor VII deficiency, acquired haemophiliac and Glanzmann's thrombasthenia.[4,5] It has also been used as an off label drug to enhance haemostasis in non haemophilic patients viz. in patients with intracerebral haemorrhage, trauma patients, retropubic prostatectomy, post partum haemorrhage and liver transplant surgeries.[6] In this case series, we present three cases of severe life threatening bleeding following caesarean section which were successfully controlled using factor VIIa.

Pregnancy is regarded as a hypercoagulable state. The normal blood loss at delivery is generally taken around 500 ml from the genital tract, after delivery of baby. It is regarded as massive when the loss is more than 1000 ml. Laboratory parameters include drop in haemoglobin concentration of 4.0 gm/dl and transfusion of more than four units of blood. Massive PPH may be due to vaginal, cervical, uterine lacerations and tears, uterine atony and inherited bleeding disorders, or due to obstetric emergencies like uterine inversion. A woman with haemoglobin level more than 11 gm/dl, can cope up with the haemorrhage, along with supportive measures. The situation worsens, when the woman is anaemic and malnourished. This blood loss can immediately transform into disseminated intravascular coagulation. PPH is regarded as a major factor in maternal mortality. Though in developed part of world, maternal mortality due to PPH has fallen viz 1 in 100,000 deliveries, where as in developing world, it is around 1 in 1000 deliveries.[1]

Measures to control PPH include both medical and surgical approaches. Medical approaches include active management of third stage of labour, use of oxytocin infusion, prostaglandins and misoprostol. Failure to control by medical measures, is followed by surgical methods. Most of the time, hysterectomy is the commonest option. Other surgical methods include arterial embolisation, B Lynch, uterine and ovarian arteries ligation, bilateral internal iliac ligation. Bilateral ligation of internal iliac arteries is not as effective as in cases of adherent placenta or as in other cases of PPH. In a series of 49 cases with severe PPH, treated with bilateral internal iliac ligation, procedure failed in patients who had received more than eight units of transfusion.[1]

Arterial embolization requires radiological intervention, and is not freely available. It also involves transferring an unstable and critically ill patient to angiography suite. Apart from these logistic loopholes, post procedure fever, feet ischaemia, bladder and rectal wall necrosis, sciatic nerve injury are the established complications of the procedure.[1]

In the above three cases we describe the use of recombinant factor VIIa for massive PPH. In two of the patients, the above factor was given as a last resort to save lives of women, when all the medical and surgical methods to control the bleeding had failed. Whereas in the third case, uterus was preserved, though medical complication of SLE was the prime reason for PPH. Unfortunately, in the first two patients fertility could not be saved. Ideally the place would have been immediately after failure of conventional medical measures. Intractable haemorrhage, following all surgical measures was the main reason to use rFVIIa to save the women's lives. Available data suggests that rFVIIa, acts rapidly, and hence serves as an effective agent in severe life threatening haemorrhage. Moreover, with higher doses of rFVIIa, peak thrombin generation is higher and is thought to result in a more stable fibrin clot formation.[7]

Bachlen F, reported a case of massive PPH treated with rFVIIa along with review of literature.[2] In thirteen reported cases which were reviewed uterine atony was present in five cases. Hysterectomy was avoided in two patients. Remaining three patients continued to bleed despite hysterectomy when rFVIIa was given as rescue treatment. In the same review rFVIIa was given in patients with DIC, and hypovolemic shock. Haemodynamic stabilization was achieved, after rFVIIa injection. The authors concluded that this new therapeutics may allow not only a decrease in the number of blood products administered, but also may avoid hysterectomy if used more rapidly.

In his editorial comments in British Journal of Anaesthesia, the editor Spahn DR commented on the role of rFVIIa before proceeding to hysterectomy.[3] Because of the rapidity of rFVIIa action it is possible to wait and observe the effect of rFVIIa before hysterectomy. The dose of the drug has been different in various case series. But the recommended dose in bleeding disorder is between 90 ug/kg to 120 ug/kg. The success of repeated dose as high as 120 ug/kg in post partum haemorrhage has also been described.[7] The drug can be given in intravenous bolus or in infusion form as well. Lower doses are required when given in infusion form.

There are risks of thrombo embolic complications with the use of rVIIa. This is due to the fact that rFVIIa is an activated factor, given in doses to raise rFVIIa level to more than 1000 fold.[7] The reported incidence of side effects is 1% in haemophiliacs but the true incidence in non-haemophiliacs is not known. But in previously healthy patients with major haemorrhage, the risk seems to be low even in the presence of DIC. But it should be used with caution in patients who are obese, have diabetes mellitus and with conditions predisposing to thrombotic complications.

Like others, we would also like to indicate a possible use of this haemostatic agent in cases of life threatening post partum haemorrhage unresponsive to conventional measures.[8,9] Ideally, appropriate trials should be conducted to define its place in massive post partum haemorrhage. But, it should be borne in mind that such trials will not be easy to perform due to difficulty to randomize such particular cases, and highly positive results in already published cases and case series.

References

1. Mousa HA, Walkinshaw S. In Major Postpartum haemorrhage. Curr Opin Obstet Gynecol 2001;13:595-603.
2. Ahonen J, Jokela R. Recombinant Factor VIIa for life threatening postpartum haemorrhage. Br J Anaesth 2005;94:592-5.
3. Sphan DR, Tucci MA, Makris M. Is recombinant factor VIIa the magic bullet in the treatment of major bleeding? Br J Anaesth 2005;94:553-5.
4. Roberts HR, Monroe DM, White GC. The use of recombinant factor VIIa in the treatment of bleeding disorders. Blood 2004;104:3858-64.
5. Kale A, Bayhan G, Yalinkaya A, Yayla M. The use of recombinant factor VIIa in a primigravida with Glanzmann's thromboasthemia during pregnancy. J Perinatal Med 2004;32;456-8.
6. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Recombinant Activated Factor V11 for acute intracerebral haemorrhage. N Engl J Med 2005;352:777-85.
7. Boehlen F, Morales MA, Fontana P, Ricou B, Irion O, Moerloose P. Prolonged treatment of massive postpartum haemorrhage with recombinant Factor VIIa: case report and review of literature. BJOG 2004;111:284-7.
8. Boouwmeester FW, Jonkhoff AR, Verheijen RH, Van Gaijn HP. Successful treatment of life threatening postpartum haemorrhage with rVIIa.Obstet and Gynecol 2003;101:1174-6.
9. Segal S, Shemesh IY, Blumenthal R, Yoffe B, Laufer N, Ezra Y, et al. Treatment of obstetric haemorrhage with R FVIIa . Arch Gynecol Obstet 2003;268:266-7.