Abstract

Postpartum hemorrhage (PPH) is a life-threatening emergency in obstetrics. In some critical cases, hemostasis is hard to achieve even after a hysterectomy has been performed. Early, effective and preferably non invasive treatments that can reduce maternal mortality and morbidity are therefore essential. Recombinant activated factor seven (rFVIIa) has been reported as a promising adjuvant therapy for obstetric hemorrhage, although it remains unlicensed for this indication. We are presenting four cases of primary PPH successfully managed using rFVIIa.

Keywords: Recombinant activated factor seven, postpartum hemorrhage, coagulopathy, blood products

1. Introduction

Pregnancy is the leading cause of death among child bearing age women worldwide and 25% of the estimated 358,000 women who die in child birth\textsuperscript{1} each year die from post partum hemorrhage (PPH). PPH occurring within 24 hours of delivery, also known as primary PPH is one of the most difficult challenges for obstetricians everywhere. The cornerstone in the treatment of PPH consists of medical management in the form of effective volume replacement, transfusion therapy, uterotonic drugs and surgical management\textsuperscript{2}. Fatal hemorrhage is most likely in circumstances in which blood and components are not available immediately.

Recently, recombinant activated factor seven (rFVIIa), a drug originally developed for treatment of hemophilic with inhibitors to factor VIII or IX, has been explored as an adjuvant therapy for hemorrhage control in various non-hemophilic bleeding situations including obstetrics and gynecology. The first successful case was reported in 2001 in a parturient without haemophilia who developed intractable, life threatening PPH as a consequence of disseminated intravascular coagulation, liver dysfunction and renal failure\textsuperscript{3}. rFVIIa is used in obstetrics in addition to conventional management, but according to the collected literature, the timing of the administration of rFVIIa for PPH is anywhere from early in treatment to a last resort. The following four cases document our experience in the use of rFVIIa in primary PPH.

2. Case No. 1

A 27 yrs old primigravida a case of ostium secondum (operated) in NYHA I not on any anticoagulant, spontaneously went into labour at 39 weeks 5 days period of gestation (POG). She underwent emergency lower segment caesarean section (LSCS) for non reassuring fetal heart rhythm. An alive female baby was delivered with Apgar of 6, 8. In the post operative room she had atonic PPH with hypotention for which caesarean hysterectomy was done following failure of medical management and a pelvic drain was left in Pouch of Doglus (POD). She was transfused 6 pints packed cell, 8 units fresh frozen plasma (FFP) during surgery. Patient was on ventilator and shifted to ICU. She developed dilutional coagulopathy with deranged coagulation parameters. Following 3-4 hrs of surgery her drain had 1.5 liters of blood. At this point of time decision to give rFVIIa was taken and 90 mcg/ kg was administered intravenously. The blood and FFP was continued,
commensurate to the haemoglobin and coagulation profile. The bleeding decreased and after about 2-3 hrs there was no more blood in the drain. She received a total of 15 packed cell and 20 FFP in the ICU. Her coagulation parameters reverted on 2nd day. She was off ventilator on 3rd day and had uneventful recovery during her post operative period.

3. Case No. 2

A 37 year Post LSCS Rh negative lady, with previous history of LSCS for abruption at 39 weeks, underwent LSCS at 38 wks 5 days POG and delivered an alive male baby with APGAR 7, 9. Patient was shifted to post op ward, 6 hrs after surgery the patient developed atonic PPH with torrential vaginal bleeding and profuse bleeding from wound of caesarean section. Resuscitation was started with crystalloids, colloids, blood and FFP. The blood loss was approximately about 2.5 litres. The coagulation profile was deranged with PT, APTT 1.5 times normal, INR was increased, inspite of all resuscitative measures the bleeding continued. Due to paucity of availability of negative blood and bleeding continuing, decision was taken to give rFVIIa. 8 units of FFP were given and rFVIIa 90 mcg/ Kg was administered. The bleeding decreased drastically within 20 mins. She had total requirement of 12 units of packed cell and 28 units of FFP and 08 cryoprecipitate. Her coagulation parameters reverted on 2nd day and discharged on 7th post operative day.

4. Case No. 3

A 20yr old primigravida at 40 weeks POG with mild gestational hypertension, underwent induction with 0.5 mg dinopristone gel. She had non-reassuring fetal heart tracings for which she underwent emergency LSCS. Following delivery she developed massive atonic PPH, unresponsive to uterotonics and bimanual massage. She was resuscitated with 2 liters of crystalloid, 4 packed cell and 8 FFP. Inspite of resuscitative measures bleeding continued, no improvement in uterine tone and hemostasis occurred. The clinical signs of haemorrhagic shock aggravated and the total blood loss was approximately 2.5 liters. rFVIIa was administered in the dose of 90mcg/ kg as an intravenous bolus. The bleeding decreased and stopped completely within 15 mins. Patient required 2 packed cell during her 01 day stay at ICU. Post operative period was uneventful and discharged on 5th post op day.

5. Case No. 4

38 yrs old with previous two normal delivery, had spontaneous vaginal delivery at 39 weeks POG and delivered a healthy male baby weighing 3.6 kg. However following delivery of placenta patient had torrential bleeding requiring rapid administration of crystalloid, colloid, blood along with uterotonic and bimanual massage. Blood loss was estimated to be approximately 2 Liters. Patient was administered 4 units of packed cell, 8 FFP, 2.5 liters of crystalloid and 1 liters of colloid. Inspite of all conservative measures the bleeding continued. At this juncture we decided to use rFVIIa and administered at 90 mcg/ kg. In 20 minutes, the bleeding got completely arrested. Post rFVIIa, she required 2 units of packed cell as haemoglobin was 7.2 gm%. She was discharged on 3rd post partum day.

All the four patient in our series had an uneventful antenatal period. In all our patients before injecting rFVIIa, we ensured a pH more than 7.2 and platelet counts upward of 50000/ mm3. All of them were discharged with haemoglobin level more than 9.2 gm%. No patients offered any signs and symptoms suggestive of deep vein thrombosis, pulmonary embolism, myocardial infarction or ischemic stroke.

6. Discussion:

Clinical reports and hematologic data, suggest improvement for more than 80% of women after rFVIIa administration and few adverse effects. The decision regarding when to use rFVII is still based on personal experience and/ or accounts from other medical specialists. Interestingly Brueckner S et al found a learning curve in the use of rFVIIa, indeed in the first part of study the average use of blood products before use of rFVIIa was 67.6 units but this fell to only 37.2 units in second part of study, indicating that rFVIIa was being administered earlier in the bleeding episode and the authors suggested that in cases of intractable PPH with no other obvious indication for hysterectomy, administration of rFVIIa should be considered before surgery.

In our case series in the first case we used rFVIIa as the last resort after cesarean hysterectomy had been performed and patient had developed coagulopathy. In the remaining three cases we restored to use rFVIIa before hysterectomy, not only was hemostasis achieved effectively, we could salvage the uterus and the requirement of blood and blood products definitely reduced. Although many experts recommend the use of rFVIIa after standard treatment has been shown to be ineffective, Clark et al believe it is equally important to avoid using rFVII as a drug of “last resort” to be used only after everything fails. In fact, patients with PPH would by this stage be so metabolically compromised that no therapy would
They therefore recommend an early intervention to control PPH at onset appears to be crucial for the success of rFVIIa. In particular, it could be worth considering its use before the decision of obstetric hysterectomy. If the indication still persists after its use, the drug will improve the course of the operation with reduction of surgery related blood loss. On the other hand, it must be stressed that rFVIIa should not be considered as a substitute for, nor should it delay, the performance of life-saving procedures such as embolisation or surgery. Furthermore, rFVIIa should not be used for an inadequate replacement therapy, and it is unlikely that it could work optimally if there is lack of basic and final components of the coagulation cascade. In all our cases an adequate replacement of blood and blood products was given before use of rFVIIa. The requirement of blood and blood products definitely reduced after its use. Some pre-requisites before using rFVIIa are shown in table 1.

Proper dosing is difficult to determine because of wide range (15-120 ug/kg) of doses reported. In our patients we had administered rFVIIa with a dose of 90 ug/ kg with adequate blood products. There have been case reports where, authors have felt, that early use of rFVIIa to control the coagulopathy prior to the emergency caesarean section may have avoided the requirement of hysterectomy, subsequent continued bleeding, second dose of rFVIIa can be used. Thus, indicating that there may be a role for pre/ intra operative use of rFVIIa in pregnant patient with liver failure, coagulopathy, and massive bleeding being taken up for emergent surgery. In our case series, we have used only a single dose of rFVIIa and which was effective in controlling the bleeding. The results or the case reports published recently do not give any evidence to extend the use of rFVIIa into less severe cases of PPH or into its prophylactic use and the dilemma whether to use the drug early or late continues.

In our series of cases we found that rFVIIa is useful in stopping the bleeding and reducing the blood product requirement. We believe that in situation of intractable PPH and where a hysterectomy is otherwise not indicated, administration of rFVIIa ought to be contemplated before performing a hysterectomy. In periphery, the amount of stored blood and blood products are less and they may not be readily available, so in severe postpartum hemorrhage it may prove as a life saving drug.

References:

Table 1: Pre-requisites for using rFVIIa

<table>
<thead>
<tr>
<th>Hemoglobin levels</th>
<th>&gt; 7gm</th>
<th>May be corrected using FFP @ 0-15 ml/kg</th>
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<tbody>
<tr>
<td>International normalized ratio</td>
<td>&lt; 1.5</td>
<td>Preferable levels &gt; 150 mg%</td>
</tr>
<tr>
<td>Fibrinogen levels</td>
<td>minimum of 100 mg%</td>
<td>2. May be corrected using cryoprecipitate @ 1-2 Units/10 kg (1 Unit/10 kg raises fibrinogen level by approx. 50 mg%)</td>
</tr>
<tr>
<td>Platelets</td>
<td>&gt; 50,000/mm3</td>
<td>May be corrected by giving platelet therapy</td>
</tr>
<tr>
<td>pH</td>
<td>≥ 7.2</td>
<td>Bicarbonate may be used to elevate the serum pH in cases of acidosis</td>
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<tr>
<td>Body temperature</td>
<td>preferably within physiological limits</td>
<td>rFVIIa retains its activity in presence of hypothermia</td>
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