Recombinant activated factor VII as a promising adjuvant therapy for postpartum hemorrhage in the practice of obstetric anesthesia: Experience from a university hospital in Taiwan

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Abstract

Massive postpartum hemorrhage is one of the major complications in the peripartum period. In some critical cases, hemostasis is hard to achieve even after a hysterectomy has been performed. Recombinant activated factor VII has been reported as a promising adjuvant therapy for obstetric hemorrhage, although it remains unlicensed for this indication. Eight cases receiving recombinant activated factor VII in postpartum hemorrhage refractory to the conventional therapy in a Taiwanese hospital were analyzed retrospectively. A good response, defined as bleeding control in 15 min, was achieved in six patients (75%) with a single dose ranging from 55 to 105 μg/kg. The two patients with a poor response were later discovered to have had unsolved birth canal injuries. No drug-related adverse effects were noted. We recommend that any surgical bleeding should first be controlled, as well as the correction of metabolic and hematological abnormalities; however, in the situation of intractable postpartum hemorrhage, recombinant activated factor VII offers a salvage therapy and should be considered early, even before hysterectomy.

Key words: coagulopathy, hysterectomy, obstetric anesthesia, postpartum hemorrhage, recombinant activated factor VII.

Introduction

Recombinant activated factor VII (rFVIIa) was developed first for the treatment of bleeding in patients with hemophilia, especially in those who have inhibitory antibodies against coagulation factors VIII or IX and thus in whom component therapy is not effective. rFVIIa is nowadays licensed as one of the standard treatments for bleeding control in hemophilia patients with inhibitors in most countries, as well as for bleeding due to acquired hemophilia, factor VII deficiency and Glanzmann’s thrombasthenia, among other conditions, in a few additional countries. In recent years, many clinicians have extended the use of rFVIIa, although unlicensed, to indications such as trauma, intracerebral hemorrhage, major surgery and massive obstetric hemorrhage. rFVIIa reduced blood loss significantly in some, but not all, situations.

Massive postpartum hemorrhage (PPH) continues to be one of the world’s leading causes of maternal morbidity and mortality. It is defined as blood loss of more than 150 mL/min (more than 50% of blood volume within 20 min), or sudden blood loss exceeding 1500–2000 mL. The conventional treatment usually starts with uterotonic agents, component therapy and fluid resuscitation. Surgical interventions, including...
repair of the genital tract, removal of retained products of conception, ligation of the uterine or internal iliac arteries, and even hysterectomy are indicated if conservative treatments fail. Sometimes, transarterial embolization (TAE) of uterine or internal iliac arteries would be an alternative choice; however, in some critical cases where coagulopathy develops as a complication from massive transfusion or amniotic fluid-related problems, hemostasis is hard to achieve, even after hysterectomy.

Recombinant activated factor VII has been applied as an adjuvant therapy for PPH in over 100 cases reported, which is promising. The first successful case was reported in 2001 in a parturient without hemophilia who developed intractable, life-threatening PPH as a consequence of disseminated intravascular coagulation, liver dysfunction and renal failure. Haynes et al. reported another four previously healthy parturients whose massive PPH was successfully treated with a single dose (70–85 μg/kg) of rFVIIa in 2002. A large series of 113 cases from nine European countries between 2000 and 2004 showed 80% marked improvement clinically and hematologically with few adverse events. Some clinicians even suggested that the earlier use of rFVIIa in PPH could reduce the need for hysterectomy; however, the majority of patient groups included in these studies were Caucasian. An investigation from Pakistan remarked that patients who received rFVIIa had lower maternal mortality and a lower number of packed red blood cell transfusions than those who did not receive the drug. Another study also suggested the effectiveness of rFVIIa in PPH among 10 Indian women. Since there is no published data regarding the Chinese population, we report our experience with a case series of eight patients receiving rFVIIa in PPH refractory to the conventional therapy in a Taiwanese hospital.

**Materials and Methods**

This is a retrospective study undertaken at the National Taiwan University Hospital, which is a tertiary referral centre in Taiwan. There were 5446 parturients, and 40 labors complicated with PPH during 2006–2009. In this case series we defined severe PPH as blood loss >150 mL/min (>50% of blood volume within 20 min), or sudden blood loss exceeding 1500–2000 mL. Eight patients received rFVIIa (NovoSeven, 1.2 mg/vial; Novo Nordisk, Bagsvaerd, Denmark) as an adjuvant therapy for severe PPH refractory to the conventional treatments. Informed consent was obtained from each patient for this off-label indication. We reviewed the medical records of these eight cases for basic data, obstetric history, treatment modalities for PPH and the response. Patient outcomes considering morbidity, mortality and any possible adverse events following rFVIIa during the hospital stay were also evaluated.

**Results**

**Basic data and obstetric history**

In the eight patients receiving rFVIIa on the indication of refractory PPH, four patients had spontaneous vaginal deliveries and the other four underwent cesarean deliveries. Uterine atony, the most common cause leading to PPH, was revealed in six patients, and birth canal injury was discovered in two cases. The rest of the causes included placenta percreta, abruptio placentae and chorioamnionitis. Disseminated intravascular coagulation was confirmed by laboratory tests (D-dimer, fibrinogen and fibrin degradation products) in five patients. Hemorrhagic shock, diagnosed clinically as tissue hypoperfusion resulting from massive bleeding with the manifestations of oliguria, decreased mental status and decreased peripheral pulses, was presented in six cases. Other major peripartum complications developed as the sequels of either emergent hysterectomy in two cases or prolonged hemorrhagic shock responding poorly to rFVIIa in another two cases. The former two cases had a urinary tract injury, which became the major problem during the postpartum course, demanding further cystorrhaphy with bilateral double-J ureter catheter insertion (cases 6 and 7). The latter included one with acute renal failure (case 1) and the other one most critically complicated (case 8) with Sheehan’s syndrome, acute renal failure and heart failure. Complex mechanical supports, such as renal replacement therapy and extra-corporeal membrane oxygenation, which was shifted to left ventricular assisted device later, were performed in this case and, as a result, the intensive care unit (ICU) and hospital stay was greatly prolonged. The patient was weaned from the mechanical circulatory supports on the eighth postoperative day (POD), transferred to the general ward on the 16th POD and discharged 45 days later. The demographic characteristics and obstetric history of these eight patients are listed in Table 1.

**Conventional intervention for PPH before rFVIIa use**

At least one uterotonic agent, oxytocin, or methylergonovine, was prescribed for all patients, and routine...
laboratory screening of coagulopathy was performed. All cases in such a life-threatening situation received massive transfusion based mainly on the clinical assessment, since the laboratory data were not available in a timely manner. In our centre, the strategy of blood replacement for critical bleeding comprises packed red blood cells, platelets and fresh frozen plasma. Cryoprecipitate is used less frequently as the first-line agent, except for those with renal failure, von Willebrand disease or hemophilia. The hematological and coagulation profiles before rFVIIa was given are listed in Table 2. As noted, the laboratory results reflected the initial condition before the empirical transfusion therapy, instead of that right before rFVIIa use. The blood component therapy before and after rFVIIa are summarized in Table 2 as well.

Surgical interventions preceded the administration of rFVIIa in six patients, including hysterectomy in four of them (Table 2). The other procedures for hemostasis comprised myomectomy, square sutures, B-Lynch sutures, uterine artery ligation and cystorrraphy; however, the bleeding could not be stopped effectively in these cases. Case 5 was the only case that achieved successful bleeding control without any surgical or radiological intervention.

rFVIIa usage: timing, dosage and clinical response

Recombinant activated factor VII was applied as a desperate attempt for these eight patients with severe PPH refractory to conventional treatment. It was applied during the operative period in six cases and in ICU in one. One case received two doses of rFVIIa in total, with one dose given in the emergency room (ER) and the second while in the operating theater.

The effect of the drug was reported by the clinicians subjectively. A good response was defined as a significant reduction in the bleeding rate within 15 min of administration; otherwise it was regarded as a poor response. A good response was observed in six out of eight patients (75%). Five of them received a single dose of rFVIIa ranging from 55–105 μg/kg body weight (average 77.13 μg/kg). In case 6, where two doses were given, a prompt response was noted after the first dose of 78.7 μg/kg, and the second dose of 39.35 μg/kg was ordered by the surgeon 25 min later for further enhancement. In the two patients with a poor response to rFVIIa, one (case 1) was finally disclosed to have a previously undiscovered anterior cervical wall injury during the radiological intervention.

Table 1. Patient characteristics and obstetric data in parturients receiving recombinant activated factor VII for major postpartum hemorrage (PPH)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Gravidity and para</th>
<th>Weeks' gestation</th>
<th>Mode of delivery and rationale</th>
<th>Major cause of bleeding</th>
<th>Major peripartum complication</th>
<th>ICU stay (days)</th>
<th>Hospital stay (days)</th>
<th>ARF (secondary to PPH)</th>
<th>Uterine atony</th>
<th>Birth canal injury</th>
<th>ARF, HF, with ECMO and VAD, Sheehan's syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>G1P0</td>
<td>39</td>
<td>NSD</td>
<td>Uterine atony, birth canal injury</td>
<td>Abruptio placentae</td>
<td>3</td>
<td>13</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>G1P0</td>
<td>36</td>
<td>CS: multiple, large transverse uterine myomas</td>
<td>Uterine atony</td>
<td>Bladder injury (secondary to surgery)</td>
<td>5</td>
<td>10</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>G1P0</td>
<td>35</td>
<td>CS: breech, twins, pre-eclampsia</td>
<td>Uterine atony</td>
<td>Bilateral ureteric strictures, hydronephrosis (secondary to surgery)</td>
<td>2</td>
<td>17</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>G2P0SA1</td>
<td>27</td>
<td>CS: twins, chorioamnionitis</td>
<td>Uterine atony</td>
<td>Bilateral ureteric strictures, hydronephrosis (secondary to surgery)</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>G6P3AA2</td>
<td>32</td>
<td>NSD: intrauterine fetal death</td>
<td>Abruptio placentae</td>
<td>Placenta percreta</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>G3P2</td>
<td>38</td>
<td>CS: placenta percreta</td>
<td>Uterine atony</td>
<td>ARF, HF, with ECMO and VAD, Sheehan's syndrome</td>
<td>6</td>
<td>16</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>G2P1</td>
<td>28</td>
<td>CS: placenta percreta</td>
<td>Uterine atony</td>
<td>ARF, HF, with ECMO and VAD, Sheehan's syndrome</td>
<td>7</td>
<td>45</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>G1P0</td>
<td>39</td>
<td>NSD</td>
<td>Uterine atony, birth canal injury</td>
<td>ARF, HF, with ECMO and VAD, Sheehan's syndrome</td>
<td>8</td>
<td>18</td>
<td>1</td>
<td>Uterine atony</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†Major peripartum complication other than disseminated intravascular coagulation and hemorrhagic shock. ARF, acute renal failure; CS, cesarean section; ECMO, extra-corporeal membrane oxygenation; HF, heart failure; NSD, natural spontaneous delivery; VAD, ventricular-assisted device.
Table 2 Management for postpartum hemorrhage (PPH) and clinical response in the eight parturients

<table>
<thead>
<tr>
<th>Case</th>
<th>Blood loss before rFVIIa (mL)</th>
<th>Coagulation profile before rFVIIa: Hb/Plt/PT/aPTT/D-d/fib</th>
<th>Timing</th>
<th>Dose No./interval</th>
<th>Dose (µg/kg)</th>
<th>Clinical response</th>
<th>Before rFVIIa</th>
<th>After rFVIIa†</th>
<th>Before rFVIIa</th>
<th>After rFVIIa†</th>
<th>Intervention for hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5000</td>
<td>7.7/77/27/27.4/&gt;200/-</td>
<td>OR</td>
<td>2/50 min</td>
<td>98.4</td>
<td>Poor</td>
<td>2/10/12/30/0</td>
<td>4/20/15/54/0</td>
<td>Hys</td>
<td>TAE</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5700</td>
<td>10.8/139/9.2/25.9/−/−</td>
<td>OR</td>
<td>1</td>
<td>57.1</td>
<td>Good</td>
<td>4/10/6/24/0</td>
<td>0/5/6/0/0</td>
<td>Surgery‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2500</td>
<td>7.1/84/9.0/31.3/−/−</td>
<td>OR</td>
<td>1</td>
<td>55.4</td>
<td>Good</td>
<td>0/4/6/30/0</td>
<td>0/2/3/6/0</td>
<td>Surgery§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3750</td>
<td>8.7/155/9.3/28.7/3.79/309.9</td>
<td>OR</td>
<td>1</td>
<td>105.3</td>
<td>Good</td>
<td>4/8/5/30/0</td>
<td>0/2/2/6/0</td>
<td>Hys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1590</td>
<td>8.8/128/14/29.9/150.5/17.7</td>
<td>ICU</td>
<td>1</td>
<td>65.4</td>
<td>Good</td>
<td>4/2/9/36/0</td>
<td>0/1/3/6/0</td>
<td>Hys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>8500</td>
<td>13.2/111/&gt;100/110.2/&gt;100/150.5/25</td>
<td>OR</td>
<td>2/25 min</td>
<td>78.7</td>
<td>Good</td>
<td>0/32/27/48/12</td>
<td>0/8/9/24/0</td>
<td>Hys, surgery¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5000</td>
<td>5.3/110/11.7/29.1/4.5/136.7</td>
<td>OR</td>
<td>1</td>
<td>91.3</td>
<td>Good</td>
<td>0/12/12/18/3</td>
<td>0/4/0/6/3</td>
<td>Hys, surgery¶</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2000, plus loss before arrival at ER from clinics</td>
<td>4/86/&gt;100/121.4/150.5/305</td>
<td>ER, OR</td>
<td>2/60 min</td>
<td>65.5</td>
<td>Poor</td>
<td>4/8/18/12/0</td>
<td>4/26/15/24/0</td>
<td>Hys</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†After 1st dose of rFVIIa. ‡Myomectomy, square suture, uterine artery ligation. §Multiple square and B-Lynch sutures. ¶Cystorrhaphy. aPTT, activated partial thromboplastin time (s); Cryo, cryoprecipitate; D-d, D-dimer (µg/mL); ER, emergency room; Fib, fibrinogen (mg/dL); FFP, fresh frozen plasma; Hb, hemoglobin (g/dL); Hys, hysterectomy; ICU, intensive care unit; OR, operating room; Plt, platelets (10⁵/µL); pRBC, packed red blood cells; PT, prothrombin time (s); rFVIIa, recombinant factor VIIa; TAE, transarterial embolization; WB, whole blood.
Use of rAFVIIa to treat PPH

following an ineffective repeated dose of 98 μg/kg. The bleeding ultimately ceased after TAE. The other case (case 8) was referred from a local hospital for severe PPH one hour after spontaneous vaginal delivery. She received the first dose of 65.5 μg/kg of rFVIIa in the ER in vain. A lateral cervical wall injury was discovered later during emergent hysterectomy. The second same dose of rFVIIa was given intraoperatively after surgical hemostasis and worked well with rapid reduction of bleeding. Nevertheless, serious complex complications arose in this case as a consequence of prolonged and profound shock, as mentioned in the previous section. The details relevant to the use of rFVIIa are summarized in Table 2.

Except for the morbidities resulting from PPH and the surgical interventions, there were no rFVIIa-related adverse events in any of the eight cases.

Discussion

Postpartum hemorrhage remains a major cause of maternal morbidity and mortality worldwide. Besides injury of birth canal, uterine atony and so on, coagulopathy due to a pre-existing condition, such as HELLP (Hemolysis, Elevated Liver enzymes, Low Platelets) syndrome or an amniotic fluid embolism, frequently contributes to major obstetric hemorrhage. The standard treatments for PPH have been outlined elsewhere; however, massive fluid resuscitation and blood transfusion might lead to hypothermia, metabolic acidosis and coagulopathy, which are the so-called ‘lethal triad’ and would further lead to a ‘vicious bloody cycle’. Postpartum hemorrhage can thus be very difficult to control once it has developed.

In recent years, an increasing number of empirical ‘off-label’ uses of rFVIIa in the treatment of massive PPH refractory to conventional methods have been reported. Data from the Italian Registry regarding 35 PPH patients receiving rFVIIa showed that the product was effective in the reduction of severe obstetric bleeding. The latest report from the Australian and New Zealand Hemostasis Registry disclosed a decrease in or cessation of bleeding in 71 of 94 obstetric patients after the final dose of rFVIIa. These accumulated successful experiences indicate that rFVIIa seems to be a potential salvage treatment for severe PPH with few adverse events.

Thrombocytopenia, hypofibrinogenemia, hypothermia and hypocalcemia have been considered responsible for the decreased activity of rFVIIa in trauma patients. The same concept has been extrapolated to PPH patients; therefore, appropriate medical interventions, such as stabilization of hemodynamic status, prevention of acidemia or hypothermia, maintenance of platelet and fibrinogen levels (>50 x 10^9/L and >1 g/L, respectively), are recommended. Detection of underlying coagulopathy by medical parameters and coagulation screening tests should also be attempted; however, in some centers, laboratory assessments are not always available quickly enough. In our centre, the initial routine assessment for critical bleeding is comprised of prothrombin time, activated partial thromboplastin time and complete blood counts. If coagulopathy is highly suspected, then fibrinogen, fibrin degradation products and D-dimer may be checked. The decision to use rFVIIa in our eight cases was based primarily on clinical assessments and laboratory parameters whenever available, and when hemorrhage was not controlled by the current accepted medical or surgical therapy.

The experiences of rFVIIa use for PPH in Asian patients are limited. In our case series of Taiwanese parturients, rFVIIa reduced the bleeding effectively in six out of eight cases and thus facilitated the restoration of tissue perfusion sooner. No drug-related adverse events were noted during the hospital stay. The good results obtained are consistent with previous reports. Concerning the two patients with a poor response to rFVIIa, unsolved birth canal injuries were later discovered and were considered to be the main reason why rFVIIa therapy failed. In one of the two cases with a poor response (case 8), although the first dose of rFVIIa failed in the ER, the second dose was given intraoperatively after hysterectomy and hemostasis was then achieved. This highlights the importance of any surgical bleeding being checked and treated first before rFVIIa use.

The optimal timing of rFVIIa administration is still an undetermined issue. In most relevant reports, rFVIIa was applied in life-threatening PPH as a desperate adjuvant after standard treatments failed. Nevertheless, Ahonen and Jokela recommended that rFVIIa should be considered before hysterectomy, especially in patients without requisite indications, such as placenta accreta. In their experience of a 12-case series, rFVIIa was given early in seven cases, none of whom then required a hysterectomy. That is particularly meaningful for women who are concerned about their fertility or body image; however, applying such an expensive and unlicensed therapy still produces some hesitation. In addition, the risk-benefit ratio may change on the occasion with only mild-to-moderate
PPH, although the current data regarding rFVIIa-related adverse reactions appears to be reassuring. In our series, the early use of rFVIIa following uterotonic agents and blood components in the ICU successfully rescued one patient and thus prevented the need for any surgical intervention. Recombinant activated factor VII was also shown to be effective in another two cases in combination with surgical procedures for uterine atony, other than hysterectomy, such as square and B-Lynch sutures. It was also used as a salvage treatment when hysterectomy failed to control bleeding in three of our cases. However, although life saving, two patients suffered from a urinary tract injury, which was a complication from the emergent operation and made the clinical course more complex. If rFVIIa could have been administered earlier, not only a hysterectomy, but also the surgery-related complications might have been prevented.

The dose of rFVIIa administered varies among reports, with a range from 15 to 120 μg/kg, and usually only a single dose is needed to produce a good result. In a large series of European patients, the most common recorded dose was $\leq 7.2$ mg, which worked out to be a dose of $\leq 90$ μg/kg, for women weighing up to 80 kg. In 80% of cases, an improvement was noticed after that single dose. Ahonen and Jokela suggested that a lower dose (42–44 μg/kg) was one of the reasons for a partial response compared with doses of 74–120 μg/kg. In our series, a rapid good response was observed in five out of eight cases with a single dose of rFVIIa ranging from 55 to 105 μg/kg. Pharmacokinetic studies have demonstrated that rFVIIa plasma clearance appears to be higher in patients with a high level of active bleeding, and this may have implications in adapting the dose regimen.

In summary, based on our own experience of an eight-case series, we suggest that rFVIIa is a promising adjuvant therapy for intractable PPH and should be considered early, even before hysterectomy, especially in patients without requisite indications, such as placenta accreta. We emphasize that any surgical bleeding should be checked and treated first before rFVIIa use. Besides, supplementation of fibrinogen and platelets preceding rFVIIa administration is essential for the greatest effect with this agent. In the setting where coagulopathy is the major contributing factor, rFVIIa offers a salvage treatment to rescue patients from life-threatening bleeding. Early use of rFVIIa would provide the potential advantage of not only uterus preservation, but also prevention of the emergent surgery-related complications, which contributes to better quality control and is also a cost saving for the hospitalization.

References