

# Use of Recombinant Factor VIIa in Gynaecology

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## Abstract

The objective of this review article was to evaluate the current literature on the unlicensed use of rFVIIa in the management of non-obstetric hemorrhage in the field of gynecology. Blood components are essential in the management of massive hemorrhage, although there is lack of evidence to guide optimal use. Prospective intervention studies, including randomized trials, are needed to clarify optimal timing and dosage of various blood components. Recombinant factor VIIa promises to be a powerful tool in managing massive obstetric hemorrhage but little is known about its potential role in controlling hemorrhage in different clinical scenarios in the non-obstetric setting. This review article is intended to draw attention from the sparse literature available to the potential use of rFVIIa in non-obstetric haemorrhage related to benign gynaecological surgery as well as gynaecology malignancy, abnormal uterine bleeding in adolescents as well as its use in Jehovah's witnesses where control of bleeding may be a clinical dilemma, in fertility and life preserving situations.

## INTRODUCTION

Recombinant Factor VIIa (rFVIIa) is the activated form of factor VII. It was first used in patients with factor VIII and factor IX deficiency who had inhibitory antibodies and in whom bleeding could not be controlled with standard replacement with blood and blood components.<sup>1</sup> At present it is licensed for use in patients with congenital haemophilias A or B and Glanzmann's thrombasthenia. It was first used successfully as an off label therapy during bleeding at caesarean delivery in 2001.<sup>2</sup> In cases of intractable bleeding before resorting to a life saving hysterectomy rFVIIa has shown effective haemostasis locally limited to the bleeding site without activating coagulation systemically at other sites.

We performed a literature (MEDLINE) search to review the relevant articles in English literature on the use of rFVIIa in non-obstetric haemorrhage in obstetrics and gynaecology. Randomized studies are usually the best way to compare different second line therapies are not available in obstetric haemorrhage as it is unlikely they will ever be performed in patients with life-threatening haemorrhage. Although there are several studies and reviews on the use of rFVIIa in obstetric haemorrhage, mainly postpartum haemorrhage; literature on the use of rFVIIa in non-obstetric haemorrhage in the speciality of obstetrics and gynaecology is very scarce.

The results of the two registries (North European<sup>3</sup> and Australia and New Zealand<sup>4</sup>) have included large obstetric series with varied management strategies for PPH; but available literature is sparse on the use of rFVIIa in non-obstetric haemorrhage.

There is substantial evidence supporting the use of rFVIIa in severe haemorrhage, in reducing the requirement of various blood-products in non-gynaecological specialties in various clinical conditions, acquired coagulopathies, liver and cardiac surgery, vascular surgery, neurosurgery, and trauma.<sup>5</sup> A large audit in cardiac surgery reported a significant reduction in the use of various blood products such as packed red cells, fresh frozen plasma (FFP), cryoprecipitate and platelets.<sup>6</sup> Another multicenter randomized placebo-controlled double-blind trial has demonstrated a noticeable decrease in use of blood products in trauma, however this study did not demonstrate a fall in mortality.<sup>7</sup>

## MECHANISM OF ACTION

The mechanism of action of rFVIIa is not clearly understood, but both a tissue factor dependant and a tissue factor-independent pathways may be involved.<sup>4</sup> Platelets are activated leading to a "thrombin burst" and formation of a strong stable clot at pharmacological doses:<sup>4</sup> Another mode of action involves activation of a fibrinolysis inhibitor

(TAFI)<sup>9</sup>. Accordingly, the effect of rFVIIa should be localized to the site of vessel injury, thus avoiding a systemic effect of widespread coagulation throughout the body.<sup>7</sup> This feature has led to its potential use in haemostasis when standard treatments have failed.<sup>8</sup>

### **USE IN GYNAECOLOGY ONCOLOGY**

There are several case reports on the efficacy of rFVIIa in controlling troublesome postoperative bleeding in gynaecology oncology.<sup>9-13</sup> A case of successful treatment of massive intra-abdominal haemorrhage complicating debulking surgery for advanced ovarian cancer has been reported.<sup>10</sup> Complete haemostasis was achieved and the woman recovered fully without any further bleeding after the administration of only two doses of rFVIIa at a dose of 20ug/kg. There are reports of successful use of rFVIIa in patients without preexisting coagulopathy who had severe bleeding from endometrial cancer and vaginal sarcoma, establishing its potential role in controlling bleeding from malignancies.<sup>11</sup> Treatment of an episode of uterine bleeding after chemotherapy in a case of acute myeloid leukemia has also been reported.<sup>14</sup> Another study has reported on its use in four postmenopausal women who underwent hysterectomy for cancer cervix, endometrial cancer and uterine fibroids where rFVIIa in a single dose less than 70 ug/kg successfully controlled bleeding within 12 hours.

Successful control of bleeding using only 2 doses in a case of metastatic cancer of the genital tract has also been reported.<sup>13</sup> Recombinant factor VIIa has been used effectively in patients with congenital FVII deficiency who had severe menorrhagia and as prophylaxis in a patient with Glanzmann's thrombasthenia undergoing surgery for a pelvic mass.<sup>15</sup> In a series of 14 cases on the use of rFVIIa in gynaecological bleeding mainly involving women undergoing surgery for gynaecological cancers; a median dose of 51.6ugm/kg was used and the median number of doses injected was 1.8.<sup>19</sup> Effective control of bleeding was achieved after conventional surgical and pharmacological measures had been tried unsuccessfully.<sup>16</sup>

### **USE IN BENIGN GYNAECOLOGY SURGERY**

There is a case report of a huge fibroid uterus of 36 weeks size with an ectopic pregnancy. Total abdominal hysterectomy was done and a massive right sided broad ligament fibroid was removed. Laparotomy was done twice-bleeding continued in spite of transfusing 75 units of blood, 40 units of fresh frozen plasma and 20 units of platelets. rFVIIa was infused prior to the third laparotomy and

bleeding decreased to allow ligation of internal iliac arteries and ensure haemostasis. The patient recovered fully after being in the ITU for 48 hours. rFVIIa helped reduce use of blood products and reduced morbidity in this case.<sup>17</sup>

### **MANAGEMENT OF ABNORMAL UTERINE BLEEDING IN ADOLESCENTS**

Clotting factor replacement with FFP or plasma derived factor concentrates, recombinant products, DDAVP or platelet transfusions have been used according to the indication. Recombinant factor VIIa is another option in adolescents with puberty menorrhagia who are not known to have bleeding disorders but have intractable life threatening bleeding unresponsive to other medical treatments. Advice from an expert haematologist can be taken in such cases before administering rFVIIa.<sup>18</sup>

### **HEREDITARY FACTOR VII DEFICIENCY IN PREGNANCY**

There is a case report of intermittent epistaxis in a case of undiagnosed hereditary factor VII deficiency, with first presentation during pregnancy at 24 weeks which was optimally managed with replacement of rFVIIa.<sup>19</sup>

### **MANAGEMENT OF GYNAECOLOGIC SURGERY IN THE PATIENT WITH FACTOR XI DEFICIENCY**

Factor XI deficiency is a rare bleeding disorder in which severity of bleeding correlates poorly with factor XI levels. Spontaneous bleeding is rare, and patients may present with a delayed onset postoperative bleed. There is a lack of standard recommendations for prophylactic treatment in cases undergoing surgery.<sup>20</sup> In patients with severe deficiency of factor XI recombinant factor VIIa has been used prophylactically in major surgery. Recombinant factor VIIa has also been used in patients when plasma derived factor XI is not available or patients decline plasma based therapy or in patients with inhibitors of factor XI.<sup>20</sup>

There is insufficient information on the standard dose and intermittent bolus doses or an initial bolus dose has been used followed by constant infusion. In a review of 10 surgical cases boluses ranging from 18 to 100ugm/kg were used with total dose of 10.8-113 mg; there were two cases of death due to acute stroke, another case of hemiparesis with stroke and a fourth case of MI. The total dose of rFVIIa used in these cases appeared to correlate with these complications. This review recommends maintaining plasma levels of factor VII at 3iu/ml for optimal haemostasis with minimal thrombotic risks.<sup>21</sup>

In another study of 5 patients with factor XI deficiency undergoing major surgery in whom rFVII was used at a higher dose of 90ugm/kg every 2 hourly for 24 hours followed by 4 hourly for next 24 hours along with oral tranexemic acid for seven days; Factor VII activity levels were 28 to 65 u/ml with trough levels from 11 to 26 u/ml. Complications ranged from local phlebitis to death in one patient. This regimen was used in four patients who underwent caesarean delivery without any complications.<sup>22</sup>

### **USE IN JEHOVAH'S WITNESSES**

There are estimated 6.5 million Jehovah's Witnesses in 235 countries. The use of blood and blood products is declined by these patients while rFVIIa may be an effective and acceptable alternative, since it is a synthetic agent. Successful use of rFVIIa along with tranexemic acid has been described in a Jehovah's Witness patient with PPH. Although there are no reports of its use in patients with intractable bleeding other than its use in PPH.<sup>23</sup> There is a potential for its use in Jehovah's Witness patients other than in cases of PPH and further studies are needed.

### **POSTOPERATIVE USE**

Recombinant factor VIIa has been successfully used in the postoperative intensive care management in patients with massive postpartum haemorrhage and also in case of persistent ooze after primary surgery and relaparotomy where the source of bleeding was not identifiable and surgical haemostasis was deemed unsatisfactory. After rFVIIa was used in these cases a decrease in surgical drain output and a significantly reduced need for blood products was observed, avoiding a need for re-exploration.<sup>24,25</sup> Recombinant factor VIIa thus has a potential role postoperatively in avoiding a relook laparotomy in cases where surgical haemostasis is deemed unsatisfactory despite of all measures, and patients are being monitored in intensive care with a possibility of a re-exploration.

### **CURRENT USAGE**

To our knowledge there is currently no strong evidence to guide clinical practice. The decision to use it is made on the advice of a haematologist; given the paucity of strong evidence for its use in obstetric haemorrhage, this can place the haematologist in a difficult position.<sup>26</sup> A multidisciplinary approach is recommended.

### **NUMBER OF DOSES AND FREQUENCY OF ADMINISTRATION**

In those cases where there has been successful control of

bleeding where other conventional methods failed; variable doses ranging from 20 to 120ugm/kg have been used which is the recommended dose in haemophiliac patients.<sup>3,27,28,29,30</sup> In most case series women received a single 90ugm/kg dose, which is the recommended dose for patients with haemophilia.<sup>3,27</sup>

Lower effective doses have been used in various published reports. Consensus recommendations for off-licensed use of rFVIIa have suggested that a mean dose of 71ugm/kg was effective in controlling bleeding.<sup>31</sup> A large series from Europe used a dose of  $\leq 90$  ug m/kg and reported a noticeable improvement after a single dose in over 80% of patients. However other reports describe lower dose of 42-44ugm/kg compared with higher doses of 74-120ugm/kg as one of the reasons for a suboptimal response.<sup>32</sup>

Due to lack of evidence in the absence of trials, and its continued off-license use, the appropriate frequency of administering repeat doses in continued bleeding is not known. Although a single dose has been most commonly used, the number of repeat doses has varied from one to eighteen and 2 hourly repeat doses can be administered in view of the short half life of rFVIIa.<sup>33</sup>

Studies have shown that rFVIIa plasma clearance appears to be higher in patients with more severe and active bleeding. Thus the dose regimen should be adapted accordingly.<sup>34</sup>

Although reduced demand for blood and blood components, haemodynamic stability and control of haemorrhage based on visual inspection are good subjective indicators;<sup>35</sup> there is no laboratory investigation to monitor clinical effectiveness. However the appropriate dose can be determined by measuring plasma levels of rFVIIa .<sup>28,29</sup>

### **TIMING OF USE**

The most appropriate timing for using rFVIIa is still a matter of individual clinical judgment, given the paucity of evidence. However early use has shown to reduce the use of blood products.<sup>34</sup> There are reports that rFVIIa should be administered when 1.5 maternal blood volumes have been lost.<sup>6</sup> In many reports, rFVII is usually a desperate last resort after standard measures have failed in a life threatening situation. This is especially relevant in cases where an earlier intervention could have proven fertility preserving rather than a desperate life saving measure. Complications due to a hastily performed life saving surgery can also be minimized by an early administration.

rFVIIa should be administered before the patient's condition becomes life threatening. Various studies have reported on the biochemical and haematological parameters to be met before rFVIIa is administered for optimal efficacy. Haemoglobin levels should be more than 7 gm/dl, INR <1.5, platelet levels should be above 50,000/cumm, fibrinogen ideally more than 150gm/dl, pH should be  $\leq 7.2$  before rFVIIa is administered as efficacy decreases at a pH of  $\leq 7.1$ . Bicarbonate may be used to correct pH and body temperature has to be optimized. The decision to use rFVIIa should ideally be taken well before metabolic parameters are deranged and irreversible complications due to hypoxia and organ injury appear.<sup>38</sup>

### SAFETY, ADVERSE EVENTS AND TREATMENT COSTS

Recombinant factor VIIa has no human protein and is not affected by availability of blood, therefore there is no risk of viral transmission. It has no anamnestic response and has a low risk of anaphylactic reactions. Its use in patients worldwide has revealed an incidence of serious adverse events less than 1% and non-serious adverse events of 13%.<sup>36</sup> Safety record in licensed indications is excellent.<sup>37</sup>

The risk of thrombosis is 25 per 100,000 infusions.<sup>38</sup> Thrombotic complications include arterial events such as myocardial infarction or ischaemia, cerebrovascular disorders and infarction of the gut; and venous thrombotic events such as pulmonary embolism and thrombophlebitis.<sup>39</sup> However these complications are rare in obstetric haemorrhage<sup>40</sup> and fall within the range expected after massive obstetric haemorrhage and DIC.<sup>3,9,18,41,42,43</sup> Thrombotic complications may be even more rare in patients with haemorrhage not related to an obstetric cause, since pregnancy by its nature is a hypercoagulable prothrombotic condition.<sup>43</sup> However concerns about thromboembolism are serious and relate more to arterial thrombotic events<sup>44</sup> hence a cautious approach with input from haematologists with expertise is required prior to its use. Minor adverse events include fever, vomiting, headache, changes in blood pressure, cutaneous hypersensitivity reactions and injections, and injection site pain. Caution is advised in the presence of disseminated malignancy and sepsis.

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High cost of rFVIIa precludes frequent and liberal dosage. However timely usage may arrest bleeding and save costs related to administration of blood and blood components, surgery and intensive care management.<sup>32</sup>

### CONCLUSION

The sparse literature available suggests that there may be a limited role for rFVIIa in managing non-obstetric haemorrhage related to gynaecology. The decision to use rFVIIa should be made with the advice of a haematologist, ideally a multidisciplinary approach is recommended.

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