

Use of recombinant factor VIIa to treat life-threatening non-surgical bleeding in a post-partum patient

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Ongoing bleeding from patients who have an acquired coagulopathy post-surgery is a common problem. Strategies that are available to combat this problem revolve around the replacement of coagulation factors, platelets, and red blood cells as necessary. These strategies are not always successful and a more direct approach to activating the coagulation system can be more effective and in some instances life saving. We describe the use of recombinant factor VIIa in a patient with ongoing post partum bleeding.

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Factor VIIa plays a central role in initiating the process of blood coagulation. It becomes active after forming a complex with tissue factor, which is located in the subendothelial media and is exposed to the circulation when blood vessels are damaged.¹ This complex then activates factors IX and X, which then induces a thrombin burst on the surface of activated platelets² and faster formation of fibrin clots at the site of vascular injury. These fibrin clots are stabilized and are resistant to premature lysis. The use of recombinant factor VIIa (rFVIIa) for treatment of intractable life-threatening haemorrhage is emerging as novel therapy for the treatment of acquired coagulopathies.¹

Case report

A 32-yr-old primigravida female underwent an emergency lower segment Caesarian section for severe fetal bradycardia (60 beats min⁻¹). This was her first pregnancy and her antepartum course had been unremarkable. She described no problems during her pregnancy, and was previously fit and well. Her arterial pressure had been recorded as between a systolic of 120–140 and 70–80 mm Hg diastolic whilst in the first stage of labour, for which she had been given nitrous oxide for analgesia. As the labour progressed, an episode of severe fetal bradycardia occurred, which led to the decision for an emergency lower segment Caesarian section to be performed. In the light of the severe bradycardia it was agreed to perform the Caesarian section under general anaesthesia, to expedite delivery of the fetus. Only before the induction of general anaesthesia was it noted that she had developed acute hypertension (170/110 mm Hg), and this was initially thought

to be because of maternal anxiety. This hypertension persisted and was initially unresponsive to increasing depth of anaesthesia (oxygen, nitrous oxide, and isoflurane with alfentanil boluses), until delivery of the fetus when hypotension (90/50 mm Hg) occurred. The cause of the hypotension was considered to be a combination of increased depth of anaesthesia, reduced surgical stimulation and probable hypovolaemia. There was no evidence of an embolic (amniotic, air, or thrombotic) cause for the hypotension, which was easily remedied with fluid therapy (500 ml colloid) and there was no change in oxygen saturation of the patient. Surgical haemostasis was achieved; blood loss was estimated at less than 500 ml and the patient's trachea extubated at the end of the procedure. In the recovery room her arterial pressure dropped to 80/60 mm Hg and she was given more fluid resuscitation: around 500 ml blood was estimated to be lost per vaginum. Blood tests at this time revealed a haemoglobin concentration of 7 g dl⁻¹, platelet count of 58×10⁹, an INR of 2.0, APTT of 45 s and D-dimers of 2.3 µg ml⁻¹. In view of her severe operative hypertension and deranged coagulation profile a possible diagnosis of pre-eclampsia complicated by disseminated intravascular coagulation (DIC), was thought to be a possibility. She was transferred to the intensive care unit for postoperative care. Further blood tests revealed deranged liver function tests, in particular raised transaminases (AST 1358 u litre⁻¹, ALT 1286 u litre⁻¹, ALP 127 u litre⁻¹, and bilirubin 35 µmol litre⁻¹), which raised the possibility of HELLP syndrome (haemolysis, elevated liver enzymes, and low platelets) and confirmed the presumptive diagnosis of rapid onset pre-eclampsia.

In the intensive care unit, the patient continued to be hypotensive (80/50 mm Hg) and she received 4 u of red blood cells, 6 u of fresh frozen plasma, and 10 u of pooled platelets. She had an increasingly distended abdomen, and became oliguric. We considered a trial of aprotinin but decided against this primarily because of our concerns that there was on-going surgical bleeding and that aprotinin administration can induce hypotension and coagulopathy. Despite being given a further 6 u of red cell concentrate and 4 u of fresh frozen plasma her haemoglobin concentration fell to 5.1 g dl^{-1} and she remained coagulopathic with an INR of 1.6, and platelet count of 38×10^9 . As the patient was still coagulopathic, her surgeons were reluctant to take her back to theatre without more evidence of bleeding: a CT scan of the abdomen confirmed the clinical picture of intra-abdominal haemorrhage.

At laparotomy, performed 12 h after the Caesarian section, 3.5 litre of blood clot and fresh blood were removed although no discrete bleeding point was discovered. Intraoperative correction of her coagulopathy continued with fresh frozen plasma (4 u), cryoprecipitate (10 u), and platelets (10 u). Fluid resuscitation intra-operatively consisted of 1000 ml of Hartmans solution and a further 3 u of red cell concentrate. On return to the ICU she remained haemodynamically stable for around 4 h but her haemoglobin fell from 8.6 to 6.2 g dl^{-1} and she lost 600 ml of blood-stained fluid from her intra-abdominal drains. Subsequently, she again became hypotensive requiring further fluid resuscitation, and became anuric. Further infusion of red blood cells, fresh frozen plasma, cryoprecipitate, and platelets led to pulmonary oedema and the development of hyperkalaemia, requiring the institution of renal replacement therapy.

With a continuing coagulopathy and exclusion of a surgical cause for on-going bleeding, we felt that a trial of recombinant factor VIIa could be of benefit. A single dose of $90 \mu\text{g kg}^{-1}$ (6 mg) recombinant factor VIIa was administered and a clinical response was apparent within 30 min. The drainage from her abdomen fell to 10 ml over the next 3 h and then stopped. Her haemoglobin concentration and arterial pressure stabilized and began to improve. There was no requirement for further red cell transfusion, but another 10 u of platelets was administered as her platelet count decreased to 30×10^9 . She required a further 6 days of intensive care during which her acute renal failure recovered. In total during her initial 24-h period on intensive care she had received 22 u of red cell concentrate, 18 u of fresh frozen plasma, 40 u of platelets, and 20 u of cryoprecipitate. Her liver transaminases, coagulation profile and platelet count had returned to normal levels by day 10 post-admission. Both mother and baby continued to do well.

Discussion

Recombinant factor VIIa was developed as a pro-haemostatic agent for the treatment of bleeding episodes in patients with haemophilia A or B with inhibitors of factors VIII or IX.³ There are reports of its successful use in non-haemophilic

patients. It has been used successfully in severe trauma,⁴ intractable bleeding after pelvic surgery,⁵ life-threatening post-partum haemorrhage,⁶ pulmonary haemorrhage,⁷ correction of coagulopathy in neurosurgical patients,⁸ and to limit bleeding in Jehovah's Witness patients after cardiac surgery.⁹ Other uses of rFVIIa include the prevention or control of bleeding in severe thrombocytopenia, platelet function disorders, and impaired liver function.¹⁰

There have been recent reports in the literature outlining the benefits of recombinant factor VIIa in obstetric disasters.¹¹ Zupanic and colleagues report the successful use of recombinant factor VIIa in massive bleeding post-Caesarian section. In this case report the patient developed evidence of HELLP syndrome in association with pre-eclampsia and also developed massive bleeding post-Caesarian section. In common with our case report their patient also responded rapidly to administration of rFVIIa.

It is important to note that the use of recombinant factor VIIa requires attention to replacement of deficient coagulation factors, red cells, fibrinogen, and platelets in addition to more general measures such as avoidance of hypothermia, acidemia, and ongoing surgical bleeding.¹² There is limited experience of the use of rFVIIa in non-haemophilic bleeding and some caution is advised with its use. Reported adverse events have included myocardial infarction, arterial thrombosis and DIC.¹³

Recombinant factor VIIa proved to be an effective agent in achieving prompt haemostasis in our patient with on-going bleeding unresponsive to the aggressive replacement of deficient coagulation factors and correction of surgical bleeding. We believe that it may become a useful adjunct in the treatment of difficult postoperative bleeding from acquired coagulopathies. This warrants further study in these situations with large numbers of patients to establish safety and efficacy of this drug in this clinical setting.

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