

CASE SERIES

Haemorrhage not Amenable to Surgery Managed Successfully with Recombinant Activated Factor VII (Novoseven)

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SUMMARY

Haemorrhage, hypothermia and acidosis are considered the triangle of death in surgical mortality. Prompt control of bleeding and adequate replacement will prevent the patient getting into an irreversible vicious cycle. We present three cases of significant bleeding not amenable to surgery and which were successfully managed with recombinant activated factor VII (rFVIIa).

Keywords: Haemorrhage, Recombinant activated factor VII

INTRODUCTION

Recombinant activated factor VII (rFVIIa) is a genetically engineered haemostatic agent used in the treatment of bleeding episodes in haemophilia A or B or who have developed inhibitors to factors VII or IX. However, rFVIIa has been increasingly used for various other types of bleeding. As most of the evidence of this off label use is in the form of case reports, all the individual experiences may well help others using this product. We had experience to use this factor to control otherwise uncontrollable bleeding due to various reasons in three cases.

CASE REPORT 1

A 24 year old female patient was admitted to the surgical casualty ward following a road traffic accident. She was cardiovascularly stable with a blood pressure of 115/70. The X-rays taken revealed fractures of the right superior and inferior pubic rami, displaced right sacroiliac joint and a compound fracture of the right lower femur. The pelvis and the femur were immobilized externally. Ultrasound scan of the abdomen showed a small amount of blood in the peritoneal cavity and a retroperitoneal haematoma extending up to the level of the symphysis pubis. She

became gradually pale and her blood pressure dropped to 80/60. She was admitted to the Intensive therapy Unit (ITU) and a second ultrasound scan of the abdomen revealed that the retroperitoneal haematoma had extended up to the umbilicus. By this time she has had 8 units of blood, 4 units of FFP and 1g of tranxemic acid.

The surgical opinion was that she was too unstable for a laparotomy and disturbing the haematoma may cause further bleeding. At this stage she was given 4.8 mg of rFVIIa. Four units of blood and two units of FFP were also transfused. Her blood pressure gradually improved with the transfusions. When her cardio-vascular status was stable, the ultrasound scan of the abdomen was repeated once again. The haematoma has not progressed any more. Her stay in the ITU for the next few days was uneventful. She was transferred to the orthopedic ward for the surgical management of her fractures.

CASE REPORT 2

An 86 year old male patient was admitted to the gastrointestinal surgical unit with a history of bleeding per rectum. He had ischemic heart disease with an ejection fraction of 25%. His Hb had been

reduced to 4g/dl. A colonoscopy was done which revealed angiodysplasia in his descending colon. Both the surgeon's and the anaesthetist's opinion was that the patient was unstable for a general anaesthetic and a laparotomy. He was managed in the ward with transfusions of packed cells, FFP and tranxemic acid without a success. He was given 4.8mg of rFVIIa. The bleeding per rectum completely stopped. The patient was discharged home few days later to be followed up in the clinic.

CASE REPORT 3

A 12 year old boy was admitted with compound fractures of the radius and the ulna of his right forearm after a fall. He had no other comorbidities. Manipulation was done under general anaesthesia and a POP cast was applied. He was discharged from hospital few days later. The child presented to the orthopedic clinic ten days later with significant pain and oedema in the affected limb. A diagnosis of compartment syndrome was made. The POP cast was cut opened following which a fasciotomy was done both anteriorly and posteriorly under anaesthesia. In the ward there was heavy oozing from the fasciotomy sites. He was taken to the operating room again the following day for exploration. No bleeders were found other than oozing from the surgical site. However the bleeding continued. The PT, INR, APTT and the platelet count were all within normal limits, and no coagulation defect was found. The child at this point had 2.4mg of rFVIIa. The oozing dramatically reduced. A second dose was given 4 hours later following which the oozing completely stopped. He had one more dose later. There was no further bleeding. After few days the fasciotomy wounds were closed. He had a re-manipulation and a new POP cast applied. The rest of his stay in the ward thereafter remained uneventful.

DISCUSSION

rFVIIa is not a replacement for a surgeon. Where surgical haemostasis has failed it can be life saving, however, rFVIIa should not be the first line of treatment. Adequate amounts of clotting factors and platelets should be available before the use of rFVIIa.

Hence the first line of treatment would be the transfusion of FFP, cryoprecipitate and platelets. It can be combined with other haemostatic agents like aminocaproic acid and tranxemic acid which were used in all of our patients. All the three patients in our case series had failed or impossible surgical haemostasis.

The Food and Drug Administration (FDA) approved rFVIIa in March 1999 for the treatment of bleeding episodes in patients with haemophilia A or B or who have developed inhibitors to factors VII or IX. This incidence of inhibitor development is around 36%.¹ In children this is as high as 50%.² It is also used in factor VII deficiency and Glanzmann thrombasthenia in some countries.³

Mode of action of recombinant activated factor VII (rFVIIa)

FVIIa binds loosely to the activated platelets. However, given in supra-physiological doses it can bind to the activated platelets and convert FX to Xa on the platelet surface.¹ This reaction which is independent of factors V, VIII, IX and XI can produce a thrombin burst sufficient enough to convert fibrinogen to fibrin. As rFVIIa acts at the site of vascular injury where TF is exposed and activated platelets are found, its action is primarily at sites of tissue damage. Given intravenously rFVIIa has a half life of approximately 2.5 hours.⁴

Off-label uses of rFVIIa

As evidenced by published literature rFVIIa has been successfully use in a variety of bleeding disorders and coagulopathies for which it has not been adequately studied.⁵ Some of the stated advantages of rFVIIa, as opposed to other haemostatic treatments (FFP, platelet concentrate, packed cells and cryoprecipitate), include a belief that since rFVIIa is not active unless it binds with TF, it will not induce systemic coagulation. Second, the activity of rFVII is not altered by the presence of clotting inhibitors. Third, there is no risk of transmission of infection since rFVIIa is not a human derived blood product. Potential off-label uses include the following.

- Variety of congenital and acquired platelet disorders
- To reverse oral anticoagulant or antiplatelet therapy
- Coagulopathy due to liver disease
- Diffuse bleeding triggered by surgery or trauma
- DIC
- As a rescue intervention in patients with intractable bleeding despite other therapeutic measures
- As prophylaxis for small bleeds at dangerous sites (e.g. liver / epidural haematoma)

It has been recommended that before the use of rFVIIa, the patient should have a fibrinogen level > 0.5g/dl and a platelet count > 50,000. As the bulk of the evidence of off-label uses is in the form of case reports and case series, we lack sufficient evidence regarding the appropriate dose for each indication, the dosing interval, whether or not to combine with other haemostatic agents (e.g. aminocaproic acid, tranexamic acid), optimal timing for use or the need for repeat doses etc.

Laboratory coagulation parameters (e.g. PT, aPTT) may be monitored together with monitoring for clinical signs of a haemostatic response. However, there is no evidence correlating achievement of haemostasis and an effect of rFVIIa on these coagulation parameters.

The recommended dose and dosing interval for rFVIIa are available for FDA approved indications (e.g. haemophilia A or B with inhibitors prior to surgery or during active bleeding). It ranges from 90-120 mcg/kg/dose every 2-4 hours.¹ At this time, there is not sufficient evidence to suggest a particular dose for off-label indications. Additionally, from the available data, there is not a clear dose response relationship for achieving haemostasis. However, one group has recommended 50-100 mcg/kg of the factor in individuals weighing 50-100

kg. While, another group has recommended a dose of 20-40 mcg/kg for anticoagulation reversal and doses of 40-90 mcg/kg for other scenarios.

It must be noted that rFVIIa may contain traces of foreign proteins from the manufacturing process, and there is a potential for a harmful antibody response in some persons.³ Inhibitors can develop against FVII. However, there are no reported cases of inhibitors developed against rFVIIa.³ Thromboembolic events (TE) correspond to 2 events /10,000. In more than 800,000 doses given TE's reported were around 1%.

CONCLUSION

Though rFVIIa is not the first line of therapy, one should not wait too long to use it either. A precise clinical judgment of the clinical situation is of utmost importance when deciding to give or not to give rFVIIa.

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