Accepted October 2014

CASE REPORT

Recombinant factor VIIa: life-saving therapy in a patient with massive bleeding and hepatic failure

I. Storms[1], M. Zijlstra[2], E.M.G. Jacobs[2], L.M. Keeris[1]

Departments of [1] Intensive Care and [2] Internal Medicine, Elkerliek Hospital, Helmond, the Netherlands

Correspondence

I. Storms – email: irisstorms@gmail.com

Keywords - **Hepatic failure, haemorrhage, factor VII deficiency, recombinant FVIIa, haematology, gastroenterology**

Abstract

The conventional management of coagulopathy in patients with massive bleeding due to acute or chronic hepatic disease is supportive, and includes fresh-frozen plasma, vitamin K and platelets. A 48-year-old male was admitted to the internal medicine ward with spontaneous bleeding of the psoas muscle combined with alcoholic cirrhosis and coagulopathy. Conventional supportive treatment, including multiple units of packed cells, fresh frozen plasma, prothrombin complex, vitamin K, fibrinogen, tranexamic acid and thrombocytes, was not effective for stopping the bleeding. Twelve days after admission, the patient developed hypovolaemic shock caused by persistent bleeding despite the conventional supportive bleeding management. The patient was admitted to the ICU. Previously conducted supplementary coagulation studies by then revealed a factor V, factor VII and antithrombin deficiency. Supportive management was continued and not effective for stopping the bleeding. A single dose of recombinant factor VIIa (90 µg/kg) was given, after which the bleeding ceased. No further therapy was necessary and the patient was discharged to the internal medicine ward. In patients with life-threatening bleeding and hepatic failure a more generalised decrease in the vitamin K dependent clotting factors must be considered, with most of the time disproportionally low levels of factor VII. In case of ongoing bleeding, despite conventional supportive therapy, recombinant factor VIIa should be considered as life-saving therapy.

Introduction

The conventional management of coagulopathy in patients with massive bleeding due to acute or chronic hepatic disease is supportive, and includes fresh-frozen plasma, vitamin K and platelets. Recombinant factor VIIa (rFVIIa) is not commonly used as a treatment of coagulopathy secondary to cirrhosis and may be a therapeutic rescue option in patients who fail to respond to the conventional therapy.

Case report

A 48-year-old male was admitted to the internal medicine ward with a painful haematoma in the right leg. The patient's medical history revealed recently clinically diagnosed hepatic cirrhosis, Child-Pugh class B (total bilirubin 118 µmol/l, reference range 3-17; albumin 23.3 g/l, reference range 35.0-48.0; international normalised ratio (INR) 1.51, reference range 0.85-1.15; prothrombin time (PT) 16 seconds, reference range 12-16; no encephalopathy and no ascites), most probably due to alcohol abuse. The patient used a proton pump inhibitor and sporadically a non-steroidal anti-inflammatory drug. He was not on any anticoagulant medication. There was a history of nicotine, alcohol and drug abuse but no history of a pre-existing coagulopathy. Laboratory evaluation on admission showed anaemia (haemoglobin (Hb) 5.5 mmol/l, reference range 8.5-11.0), thrombocytopenia (thrombocytes 70x109/l, reference range 150-400), a mildly elevated prothrombin time (PT 16 seconds, referance range 12-16) and a normal activated partial thromboplastin time (APTT, 30 seconds, reference range 23-33) *(table 1)*.

Abdominal ultrasound and computed tomography (CT) showed right-sided bleeding of the psoas muscle and signs of cirrhosis as gastric varices and splenomegaly. The initial diagnosis was spontaneous psoas bleeding in a patient with alcoholic cirrhosis, Child-Pugh class B.

Further diagnostic tests and complementary coagulation studies were applied. Active viral infections such as cytomegalovirus, Epstein-Barr virus, hepatitis A, hepatitis B, hepatitis C, syphilis *(Treponema pallidum)* and human parvovirus B19 were excluded. During the following days on the internal medicine ward the patient remained in a stable condition and received supportive therapy: vitamin K (orally and intravenously), prothrombin complex concentrate, packed cells, fresh frozen plasma, fibrinogen, tranexamic acid and platelets. We corrected the Hb to >5.0 mmol/l, thrombocytes to >100x109/l, INR to 1.26 and the APTT normalised.

Table 1. Laboratory evaluation on admission to the internal medicine ward

Laboratory test	Blood level	Reference range
Total bilirubin	118	3-17 µmol/l
Conjugated bilirubin	37	10-13%
Alkaline phosphatase	233	40-115 U/l
Gamma-glutamyltransferase	55	0-55 U/l
Aspartate aminotransferase	116	0-35 U/l
Alanine aminotransferase	36	0-45 U/l
Lactate dehydrogenase	400	0-248 U/l
Albumin	23.3	35.0-48.0 g/l
Haemoglobin	5.5	8.5-11.0 mmol/l
Haematocrit	0.26	0.40-0.50 l/l
Mean corpuscular volume	106	80-100 Fl
Thrombocytes	70	150-400 x109 /l
Activated partial thromboplastin time	30	23-33 seconds
Prothrombin time	16	9-12 seconds

Twelve days after admission our patient deteriorated and developed hypovolaemic shock. We suspected an abdominal bleeding focus; therefore, a CT scan of the abdomen was performed which revealed a bleeding psoas with intra-abdominal breakthrough. Because of acute kidney injury (creatinine 212 µmol/l, reference range 54-105), no intravenous contrast was used, so active bleeding could not be excluded. Angiography and radiographic coiling were discussed, but as the patient seemed to stabilise haemodynamically during the initial resuscitation they were not performed.

The patient was admitted to the ICU. Despite continuation of the supportive therapy there were persisting signs of ongoing bleeding by declining haemoglobin levels, without haemodynamic consequences. Subsequent transfusion remained needed. Previously conducted supplementary coagulation studies became available and revealed deficiencies in factor V (factor V activity 48%, normal range 60-140%), factor VII (factor VII activity 25%, normal range 60-140%) and antithrombin (27%, normal range 80-120%). There was an increase in the Von Willebrand factor activity (310%, normal range 60-140%).

Because of the patient's history of substance abuse, intoxication with vitamin K antagonist was tested and excluded. Hepatic failure was concluded to be the most probable cause of the clotting factor deficiencies. As the bleeding caused no haemodynamic problems, coiling was not discussed again. The literature was reviewed searching for clues to stop the bleeding by other conservative ways as the treatment chosen was insufficiently proven by the amount of packed cells needed each day. Here clues were presented of safe use of recombinant factor VIIa (rFVIIa) in patients with chronic liver disease and bleeding disorders. In consultation with the hospital haematologist a single dose of rFVIIa (90 µg/kg) was given, after which the bleeding stopped. No further therapy was necessary and the patient was discharged to the internal medicine ward *(figure 1)*.

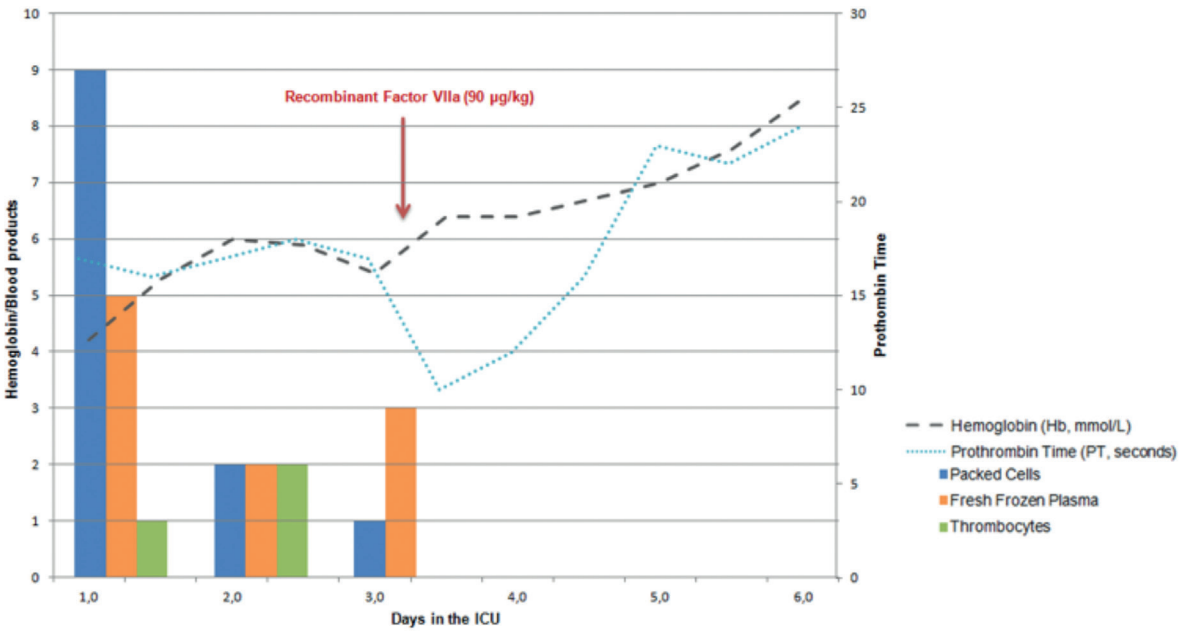
Discussion

Coagulation problems in liver disease are multifactorial.[1] In patients with liver disease there is a disturbed haemostasis balance of procoagulant and anticoagulant factors. Elevated procoagulant factors are Von Willebrand factor and factor VIII, whereas there is a decrease in the procoagulant factors protein C, protein S, antithrombin and plasminogen. Anticoagulant factors are decreased as shown by thrombocytopenia, abnormal platelet function, low levels of factor II, V, VII, IX, X and XI, vitamin K deficiency and dysfibrogenaemia. This disturbance explains why patients with liver disease are susceptible for thrombotic as well as bleeding complications.[2,3] Coagulant disorders vary according to the aetiology of the liver failure. For instance in acute liver failure thrombocytopenia is less common, whereas the decrease in plasma levels of coagulation factors is more severe in comparison with chronic liver failure. In cirrhosis normal fibrinolysis or hyperfibrinolysis is present, but in acute liver failure fibrinolysis is inhibited.[2] Unfortunately the routine haemostasis tests such as platelet count, PT and APTT are not indicative for these changes in the haemostatic balance, making treatment of coagulation disorders in liver failure challenging.[2,3]

Factor VII (FVII) is a vitamin K dependent glycoprotein which consists of 406 amino acids and is synthesised in the liver. In vascular injury, tissue factor is released which binds to activated FVII (FVIIa) and further activates the coagulation cascade. About 1% of the circulating factor VII (FVII) is activated; backward activation further activates more FVII. A FVII deficiency can be hereditary or acquired.[4] The estimated prevalence of an inherited or congenital FVII deficiency is between 1:300,000 and 1:5,000,000.[4]

Acquired FVII deficiency can have different aetiologies.[4] The most common case is acquired vitamin K deficiency caused by the use of vitamin K antagonists such as acenocoumarol and warfarin.[4] Chronic liver disease is the second most common cause of acquired FVII deficiency. In hepatic disease a deficiency of all vitamin K dependent clotting factors (factor II, VII, IX and X, protein C and S) is expected, but usually the levels of FVII are disproportionally low compared with other vitamin K dependent clotting factors. Hepatic syndromes such as Dubin-Johnson syndrome, Rotor syndrome and Gilbert syndrome are also associated with low FVII levels.[1,4-7] Rarer causes of FVII deficiency include the development of FVII inhibitors secondary to drugs, malignancy and sepsis.[4] In our patient there was no evidence of one of these causes as an explanation for the FVII deficiency.

Figure 1. Course of haemoglobin, prothrombin time and number of blood products during the ICU stay



The spectrum of bleeding problems in a FVII deficiency is variable, and ranges from epistaxis to gastrointestinal bleeds, muscle bleeds, joint bleeds and as worst-case scenario central nervous system bleeds. Muscle bleeds are seen in 20% of the cases. For unknown reasons there is a poor correlation between the measured level of FVII and the risks of bleeding.[4]

The management of bleeding problems in cirrhosis is purely supportive and includes fresh-frozen plasma, vitamin K, tranexamic acid and platelets.[1,4-7] However, in case of failure of conventional supportive therapy, rFVIIa can be life-saving. The precise mechanism at this point is unclear.[1,4-13]

In patients receiving rFVIIa for off-label indications there is limited evidence regarding the risk of complications. The available evidence at this point in time reports no increased risk of venous and arterial thromboembolism.[14-16]

Conclusion

In patients with hepatic failure and life-threatening bleeding a generalised decrease in vitamin K dependent clotting factors is present, often with disproportionally low levels of FVII. In case of ongoing bleeding, despite conventional supportive therapy, rFVIIa should be considered life-saving therapy. The mechanism of action has not yet been discovered. Further research in the off-label use of rFVIIa regarding efficacy, dose, complications and costs is necessary.

Disclosure

The authors declare no conflict of interest.

References

1. Caldwell SH, Hoffman M, Lisman T, et al. Coagulation in Liver Disease Group. Coagulation disorders and hemostasis in liver disease: Pathophysiology and critical assessment of current management. Hepatology. 2006;44:039-46.
2. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. Blood. 2010;116:878-85.
3. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. N Engl J Med. 2011;365:147-56.
4. Perry DJ. Factor VII Deficiency. Br J Haematol. 2002;118:689-700.
5. Caldwell SH, Chang C, Macik BG. Recombinant activated factor VII (rFVIIa) as a hemostatic agent in liver disease: A break from convention in need of controlled trials. Hepatology. 2004;39:592-8.
6. Shami VM, Caldwell SH, Hespenheide EE, Arseneau KO, Bickston SJ, Macik BG. Recombinant activated factor VII for coagulopathy in fulminant hepatic failure compared with conventional therapy. Liver Transpl Surg. 2003;9:138-43.
7. Bernstein D. Effectiveness of the recombinant factor VIIa in patients with the coagulopathy of advanced Child's B & C cirrhosis. Semin Thromb Hemost. 2000;26:437-8.
8. White B, Martin M, Kelleher S, Browne P, McCann SR, Smith OP. Successful use of recombinant FVIIa (Novo seven) in the management of pulmonary haemorrhage secondary to Aspergillus infection in a patient with leukaemia and acquired FVII deficiency. Br J Haematol. 1999;106:254-5.
9. Meaudre E, Kenane N, Kaiser E, et al. Isolated acquired factor VII deficiency in patient with severe head trauma: use of factor VII (factor VII-LFB). Ann Fr Anesth Reanim. 2005;24:1383-6.
10. Mullighan CG, Rischbieth A, Duncan EM, Lloyd JV. Acquired isolated factor VII deficiency associated with severe bleeding and successful treatment with recombinant FVIIa (Novoseven). Blood Coagul Fibrinolysis. 2004;15:347-51.
11. Scharrer I. Recombinant factor VIIa for patients with inhibitors to factor VIII or IX or factor VII deficiency. Haemophilia. 1999;5:253-9.
12. Muleo G, Santoro R, Iannaccaro PG, Papaleo P, Leo F. The use of recombinant activated factor VII in congenital and acquired factor VII deficiencies. Blood Coagul Fibrinolysis. 1998;9:389-90.
13. Spahn DR, Tucci MA, Makris M. Is recombinant FVIIa the magic bullet in the treatment of major bleeding? Br J Anaesth. 2005;94:553-5.
14. Pham HP, Hsu SX, Parker-Jones S, Samstein B, Diuguid D, Schwartz J. Recombinant activated factor VII in patients with acute liver failure with UNOS Status 1A: a single tertiary academic centre experience. Vox Sang. 2014;106:75-82.
15. Yank V, Tuohy CV, Logan AC, et al. Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. Ann Intern Med. 2011;154:529-40.
16. Logan AC, Goodnough LT. Recombinant factor VIIa: an assessment of evidence regarding its efficacy and safety in the off-label setting. Hematology Am Soc Hematol Educ Program. 2010;2010:153-9.