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

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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.

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, reference 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 thrombocytes. We corrected the Hb to >5.0 mmol/l, thrombocytes to >100x10⁹/l, INR to 1.26 and the APTT normalised.

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.
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. 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. 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. 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.

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 cascade consists of 406 amino acids and is synthesised in the liver.

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

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