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**Control of variceal bleeding in a patient with severe
haemophilia A and factor VIII inhibitors using a
Transjugular Intrahepatic Portosystemic Shunt [TIPPS]**

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4 **Control of variceal bleeding in a patient with severe haemophilia A and factor VIII**
5 **inhibitors using a Transjugular Intrahepatic Portosystemic Shunt [TIPPS]**
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11 Dear Editor,

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13 Many patients with haemophilia became infected with hepatitis C virus [HCV] prior to
14 the introduction of virus inactivated clotting factors and have subsequently developed
15 progressive liver disease including cirrhosis. Cirrhosis leads to the development of
16 portal hypertension, which is associated with a risk of variceal haemorrhage. This
17 complication of cirrhosis is particularly challenging in patients with bleeding disorders,
18 especially those with inhibitors. UK guidelines recommend that variceal haemorrhage
19 should be managed initially with endoscopic band ligation or sclerotherapy, followed by
20 the insertion of a transjugular intrahepatic portosystemic shunt [TIPSS] for uncontrolled
21 bleeding. [1] The insertion of a TIPSS has previously been described in patients with
22 haemophilia [2] but not in a patient with a high titre inhibitor.
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37 We report a 71 year old man with severe haemophilia A complicated by a high titre
38 FVIII inhibitor [150 Bethesda Units] who presented with haematemesis and
39 haemodynamic compromise. He was known to have chronic HCV viraemia [HCV RNA
40 positive by PCR] with cirrhosis and had previously presented with upper GI bleeding
41 secondary to oesophageal varices. He had previously been managed with propranolol
42 and multiple endoscopic banding sessions. Anti-viral therapy for HCV and liver
43 transplantation had both been discussed with the patient previously and declined.
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56 Initial investigations revealed Hb 9.9 g/dl, WCC $16.6 \times 10^9/l$, Platelets $290 \times 10^9/l$, PT 15s,
57 APTT 128s and Fibrinogen 2.4 g/L. He was managed with fluid resuscitation, blood
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4 transfusion, recombinant factor VIIa [rFVIIa 90µg/kg] every two hours, intravenous
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6 proton pump inhibitor, glypressin, tranexamic acid and antibiotics. He required a six-
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8 unit blood transfusion at presentation. The patient underwent endoscopy with variceal
9
10 sclerotherapy but, despite these interventions there was evidence of on-going active
11
12 haemorrhage. The patient was discussed with the hepatologists who recommended
13
14 urgent TIPSS insertion.
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21 Prior to TIPSS insertion the dose of rFVIIa was escalated to 180µg/kg, in addition to the
22
23 2 hourly dose of 90µg/kg which was maintained until six hours post procedure when it
24
25 was reduced to 3 hourly. Also prior to the procedure the patient required further
26
27 transfusion support with blood, platelets (as platelet count had dropped to $79 \times 10^9/l$) and
28
29 cryoprecipitate (as fibrinogen had dropped to 1.0 g/l).
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35 The TIPSS successfully reduced the portosystemic gradient from 15-16mmHg pre-
36
37 procedure to 6-8mmHg post-procedure. Unfortunately the patient suffered a further
38
39 large episode of haematemesis the day following the TIPSS insertion. The hepatologists
40
41 recommended no further intervention and that the prognosis was poor. Given the
42
43 severity of the situation factor VIII inhibitor bypassing activity [FEIBA®] at a dose of
44
45 4000 units [50 Units/Kg] twice a day was added to his treatment. Following this
46
47 addition there were no further episodes of bleeding. Four days into combined FEIBA®
48
49 and rFVIIa therapy the patient developed compensated DIC. [PT 15s, APTT 85s,
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51 Fibrinogen 0.9g/l, D-dimer 6.84mg/l] At this time the rFVIIa dose intervals were
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53 increased the FEIBA® continued twice daily for three more days. There was no further
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55 bleeding and the fibrinogen and D-dimer levels normalised.
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4 Following a period of rehabilitation the patient was discharged home. The patient
5
6 continued to receive regular follow up which included α fetoprotein and ultrasound
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8 screening. Seven months post TIPSS insertion the patient's α fetoprotein began to climb
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10 and multifocal hepatocellular carcinoma was diagnosed. The patient died 2 years later
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12 from this complication but he suffered no further episodes of upper GI bleeding.
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19 The use of TIPSS to manage variceal bleeding when endoscopic therapy has been
20
21 unsuccessful is now considered a standard treatment. [1] The safety of TIPSS insertion
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23 in patients with haemophilia has been evaluated by others and although the numbers
24
25 reviewed were small the efficacy seems to be comparable with the non-haemophiliac
26
27 population.[2] Therefore this therapeutic option can be life saving for haemophiliac
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29 patients including those with inhibitors, as we have demonstrated in this case report.
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35 The management of acute bleeds in haemophilia A patients with inhibitors is
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37 challenging. There are numerous methods used to control bleeding which have been
38
39 evaluated in a recent systematic review [3]. This review recommended the use of high
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41 dose factor VIII first line but this was not appropriate for our patient due to the presence
42
43 of high inhibitor antibody levels. Alternatives for our patient would be rFVIIa or an
44
45 activated prothrombin concentrate [FEIBA®]. Our patient had previously had upper GI
46
47 bleeds managed effectively with rFVIIa and therefore this therapy was used first line.
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49 When bleeding continues following the TIPSS procedure the haemostatic support was
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51 intensified, using a combination of both FEIBA® and rFVIIa, in view of the life-
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53 threatening nature of the situation.
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4 The use of combination therapy is considered experimental. There is a theoretical
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6 increased risk of thrombogenic complications with combination therapy. Thrombotic
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8 events with single therapies have been described, mainly myocardial infarction or DIC,
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10 but they are rare. [4] Others have successfully used combination therapy with good
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12 clinical benefit and no increase in adverse events. [5] However, our patient developed
13
14 hypofibrinogenaemia which probably represented compensated DIC or may have been
15
16 due to an element of hyperfibrinolysis. It is not clear if this complication was due to the
17
18 combination of haemostatic therapies, the transfusion support provided or related to his
19
20 underlying disease. One possibility is that our patient received antifibrinolytic therapy,
21
22 tranexamic acid, throughout his illness in addition to combination therapy, which may
23
24 account for the development of the laboratory abnormalities in our patient. With close
25
26 monitoring in a specialist facility the thrombotic complications of this triple therapy
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28 were successfully managed and the patient made an excellent recovery indicating that in
29
30 life threatening bleeding this aggressive treatment of bleeding should be considered.
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15 9th June 2009-06-09

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20 Dear Sir/Madam,

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24 I am writing on behalf of my co-authors and I to confirm that the attached case report has
25 not been published in any other journals and has not been submitted for consideration of
26 publication to any other journal.
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36 Yours faithfully,

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43 **Dr. Erin Hurst**
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Full Title

A Case report of the control of variceal bleeding in a patient with severe haemophilia A and factor VIII inhibitors using a Transjugular Intrahepatic Portosystemic Shunt [TIPPS]

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Running Title

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