CLINICAL CASE

Transcatheter local thrombolysis in patients with extensive TIPS thrombosis

La thrombolyse par voie locale chez les patients avec thrombose extensive du TIPS

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Available online 12 October 2010

Summary

\textbf{Background.} — Transcatheter local thrombolytic therapy in patients with portosplanchnic venous thrombosis has been used in few cases.

\textbf{Case reports.} — Here, we present our single-center experience with transcatheter thrombolytic therapy in three patients with extensive refractory portal and transjugular intrahepatic portosystemic shunt (TIPS) thrombosis. Thrombolytic therapy was successful for all three patients. Two patients developed minor procedure-related bleeding.

\textbf{Conclusion.} — Local thrombolysis could be proposed in case of TIPS thrombosis for patients in whom the venous flow cannot be restored by using conventional anticoagulant therapy and stent mechanical revision.

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Transjugular intrahepatic portosystemic shunt (TIPS) is used to create a low-resistance channel between the hepatic vein and the intrahepatic portion of the portal vein by deployment of an expandable metal stent \cite{1}. During the past 20 years, TIPS has been used for many indications: variceal bleeding (acute variceal bleeding, prevention of rebleeding, treatment of ectopic varices, primary prophylaxis of variceal bleeding, portal hypertensive gastropathy), ascites (refractory ascites, hepatorenal syndrome types 1 and 2, hepatic hydrothorax, closure of umbilical hernia), Budd-Chiari syndrome, veno-occlusive disease, non-cavernomatous portal vein thrombosis, portal hypertension in malignancies, treatment of portal hypertension prior to gastrointestinal surgery or liver transplantation \cite{2}. Shunt occlusion may occur at any time during follow-up, thus suitable monitoring of shunt function is mandatory and easily made using Doppler ultra-
sonography [3]. Early shunt thrombosis can probably be avoided by anticoagulation [4]. In addition, trapidil and ticlopidine with initial heparin reduced intimal proliferation [5]. Recently, the use of expanded polytetrafluoroethylene (ePTFE)-covered stents resulted in improved primary patency rate [6]. Shunt mechanical revision is performed on clinical needs, thus reappearance of varices or ascites. We report here three cases of patients who presented refractory extensive TIPS and portal thrombosis, treated with local transcatheter thrombolysis.

Case reports

Patient 1

In October 2008, a 47-year-old woman was referred to our institution because she presented alcoholic cirrhosis complicated by portal hypertension and refractory ascites, needing iterative paracentesis since five months. Alcohol consumption was stopped since five months. In the absence of contraindication, a TIPS was placed in October 2008 in the right hepatic vein, and the immediate postoperative course was uneventful. The efficiency of the TIPS was regularly checked by Doppler ultrasonography with Sonovue® (Altana Pharma, Le Mée-sur-Seine, France) injection (October 2008, November 2008 and January 2009), disclosing the complete regression of ascites and the patency of the stent. In February 2009, she was readmitted for acute abdominal pain. Upon admission, the patient complained of abdominal pain with general malaise and confusion. Physical examination found flapping tremor and ascites. The ascites fluid was sterile. The abdominal CT scan showed thrombosis of the portal system extending from the splenomesenteric confluence to the portal vein associated to a massive intra peritoneal epanchment. Anticoagulation treatment by heparin was started. After two weeks, because of persistent TIPS thrombosis, a mechanical revision of TIPS was realised, associated with the placement of a portal catheter for delayed local thrombolytic therapy, because of persistent extensive thrombosis at the end of the procedure. Recombinant tissue type plasminogen activator (Actilyse®, Boehringer Ingelheim France, Reims, France) was used as thrombolytic agent and was delivered by means of the locally placed catheter. The patient was treated by continuous infusion of 2 mg/hour rtPA, preceded by 4 mg bolus injection. In addition to thrombolytic treatment, anticoagulation treatment by heparin was maintained. The thrombolytic agent was stopped after 12 hours because the patient developed multiple minor bleeding and the laboratory evaluation showed a marked decrease of fibrinogen inferior to 1 g/L. The clinical course was favourable: the stent was permeable at 24 hours after thrombolysis initiation, and abdominal pain, ascites and hepatic biological abnormalities disappeared within a few days. An abdominal CT scan realised after seven days showed the total disappearance of the thrombus. The efficiency of the TIPS was therefore regularly checked by Doppler ultrasonography with Sonovue® injection (April 2009, May 2009 and July 2009), disclosing the complete regression of ascites and the patency of the stent. Anticoagulation with nadroparine was maintained until July 2009, and stopped thereafter. After stopping anticoagulation, exhaustive search of an underlying thrombophilic state was performed to explain the occurrence of extensive portal thrombosis in our patient. Specific tests for paroxysmal nocturnal haemoglobinuria, lupus anticoagulant and antiphospholipid antibodies, deficiency in protein S, antithrombin III or plasminogen, factor V Leiden MTHFR and G20210A factor II gene mutations, were all negative. The serum homocystein concentration was also normal. Finally, a protein C deficiency was diagnosed (26% with normal prothrombin index).

Patient 2

In April 2002, a 48-year-old man was first referred to our institution because of acute variceal bleeding complicating alcoholic cirrhosis. At that time, treatment consisted in variceal band ligation and propranolol, leading to eradication of esophageal varices, after five sessions. Alcohol consumption was maintained. Regular follow-up was uneventful. In March 2008, he presented a second complication of portal hypertension, i.e. ascites, needing iterative paracentesis despite high doses of diuretics. In September 2008, in the absence of contraindication, a TIPS was placed in the right hepatic vein. Immediately, anticoagulation treatment by heparin was started and maintained thereafter. The efficiency of the TIPS was checked by Doppler ultrasonography with Sonovue® injection, disclosing early stent thrombosis. A mechanical revision of TIPS was realised, but failed to obtain stent patency. A new procedure was performed in December 2008, leading to a second TIPS insertion in the median hepatic vein. The efficiency of the TIPS was regularly checked by Doppler ultrasonography with Sonovue® (December 2008, January 2009 and May 2009), disclosing stent patency and significant reduction of ascites (paracentesis were not necessary during this period). In June 2009, he was readmitted for massive recurrent ascites and confusion. Ascites fluid infection was diagnosed and antibiotics were started. Abdominal CT scan showed thrombosis of the portal system extending from the splenomesenteric confluence to the portal vein associated to an intraperitoneal epanchment. A mechanical revision of TIPS (median hepatic vein) was realised, associated with the placement of a portal catheter for delayed local thrombolytic therapy, because of persistent thrombosis at the end of the procedure. Recombinant tissue type plasminogen activator (Actilyse®) was used as thrombolytic agent and was delivered by means of the locally placed catheter. The patient was treated by continuous infusion of 2 mg/hour rtPA, preceded by 2 mg bolus injection. In addition, anticoagulation treatment by heparin was maintained. The thrombolytic agent was stopped after six hours because the patient developed multiple minor bleeding and the laboratory evaluation showed a marked decrease of fibrinogen inferior to 1 g/L. The clinical course was favourable: the stent was permeable at 24 hours after thrombolysis initiation. Ascites progressively improved under diuretic therapy. An abdominal CT scan realised after eight days showed the total disappearance of the thrombus. Anticoagulation with nadroparine was maintained. The efficiency of the TIPS was therefore regularly checked by Doppler ultrasonography with Sonovue® injection (July 2009 and August 2009), disclosing regres-
sion of ascites and patency of the stent. In November 2009, the patient was admitted for severe liver failure. Alcohol consumption was still maintained. Doppler ultrasonography disclosed recurrent TIPS thrombosis. Non-adherence to medical treatment (diuretics, anticoagulant...) was suspected from patient’s family questioning. Clinical evolution was unfavourable and the patient died in January 2010.

**Patient 3**

In July 2008, a 52-year-old man was referred to our institution because he presented alcoholic cirrhosis complicated by portal hypertension and refractory ascites, needing iterative paracentesis since three months. The diagnosis of cirrhosis was made in May 2008 at the time of upper gastrointestinal haemorrhage due to variceal rupture, treated by band ligation (three sessions). Alcohol consumption was stopped since three months. In the absence of contraindication, a TIPS was placed in January 2009 in the right hepatic vein, and the immediate postoperative course was uneventful. The efficiency of the TIPS was regularly checked by Doppler ultrasonography with Sonovue® injection (January 2009 and February 2009), disclosing partial regression of ascites and the patency of the stent. In April 2009, Doppler ultrasonography with Sonovue® disclosed partial thrombosis of the stent, associated with majoration of ascites. The ascites fluid was sterile. Anticoagulation treatment by heparin was started and a mechanical revision of TIPS was realised. One month after revision, Doppler ultrasonography with Sonovue® and abdominal CT scan showed thrombosis of the TIPS and the portal vein associated to a massive intraperitoneal epanchment, despite anticoagulation. A second mechanical revision of TIPS was realised, associated with the placement of a portal catheter for delayed local thrombolytic therapy, because of persistent extensive thrombosis at the end of the procedure (Fig. 1). Recombinant tissue type plasminogen activator (Actilyse®) was used as thrombolytic agent and was delivered by means of the locally placed catheter. The patient was treated by continuous infusion of 2mg/hour rtPA, preceded by 4mg bolus injection. In addition to thrombolytic treatment, anticoagulation treatment by heparin was maintained. The thrombolytic agent was stopped after 48 hours because the clinical course was favourable and the stent was permeable at 24 hours after thrombolysis initiation. Ascites disappeared within two weeks. An abdominal CT scan realised after two weeks showed the total disappearance of the thrombus. The efficiency of the TIPS was therefore regularly checked by Doppler ultrasonography with Sonovue® injection (July 2009, August 2009, October 2009 and January 2010), disclosing the complete regression of ascites and the patency of the stent. Anticoagulation with nadroparine was maintained until October 2009, and stopped thereafter. After stopping anticoagulation, exhaustive search of an underlying thrombophilic state was performed to explain the occurrence of extensive portal thrombosis in our patient. Specific tests for paroxysmal nocturnal haemoglobinuria, lupus anticoagulant and antiphospholipid antibodies, deficiency in protein S, protein C, antithrombin III or plasminogen, factor V Leiden MTHFR and G20210A factor II gene mutations, were all negative. The serum homocystein concentration was also normal.

**Discussion**

We report here the cases of three patients who experienced extensive thrombosis of TIPS and portal system, requiring local thrombolytic therapy. In all three cases, treatment was successful, with delayed recurrent thrombosis in one patient.

It is now well recognized that splanchnic thrombosis most often occurs when a local and systemic risk factor is associated. An association between local and systemic aetiological factors of portal vein thrombosis is present in one fourth of the cases [7], and when a local risk factor is identified, an associated prothrombotic systemic disorder is present in 70% of cases [8]. The main local factor includes inflammations of the abdomen, hepatobiliary malignancies, disorders leading to a decrease in portal flow, or endothelial lesions which initiate thrombus formation, such as trauma or surgical injury. Systemic risk factors include prothrombic disorders or underlying haematological diseases that predispose to hypercoagulability, such as myeloproliferative diseases and paroxysmal nocturnal haemoglobinuria.

The major long-term drawback of TIPS is undoubtedly stent dysfunction due to occlusion or stenosis. It can be estimated that reintervention to reestablish or maintain the patency of the shunt is required in 70–90% of patients, within two years of TIPS insertion, including total occlusion in 20–40% of the patients. Nevertheless, the secondary patency rate after revision during a two- to five-year follow-up period is between 72 and 91% [1,2,9–12]. As a result, in some cases, stent patency cannot be restored. Our results reported here suggest that local thrombolysis can probably be proposed in such cases.

During the past decade, both systemic and local (intraarterial or intravenous) administration of thrombolytics have been described in the treatment of hepatic and/or splanchnic venous thrombosis, associated in some cases

![Figure 1](Image)

**Figure 1** Angiography (transjugular portography) showing persistent thrombosis of the intrahepatic stent after mechanical revision.
with TIPS insertion [13—25]. Very recently, Smalberg et al. reported a large single-center experience with transcatheater thrombolytic therapy in 12 patients, including six patients with Budd-Chiari syndrome (associated TIPS insertion in three cases), four patients with portal vein thrombosis (associated TIPS insertion in one case) and two cirrhotic patients with TIPS thrombosis [25]. Thrombolytic therapy was successful in three cases and partially successful in four cases. In addition, two patients developed minor procedure-related bleeding (17%) and six patients (50%) developed major procedure-related bleeding, with a fatal outcome in two. In this series, the high rate of complication could be due to associated transhepatic manoeuvres, such as TIPS insertion in the majority of the cases. At the present time, thrombolytic agents are used in many clinical situations, including acute myocardial infarction, acute ischemic stroke, peripheral arterial occlusion, pulmonary embolism, and deep vein thrombosis. For example, from trials including patients randomized to thrombolytic therapy versus control therapies in suspected acute myocardial infarction, an excess of 10% in overall hemorrhagic complications and of 2% in major bleeding (life-threatening or requiring blood transfusion), including a half of intracranial hemorrhage, is expected [26,27]. Risk factors for hemorrhagic complications of thrombolysis include increasing age, lower body weight, female gender, uncontrolled hypertension, recent stroke or surgery, the presence of a bleeding diathesis, and severe congestive heart failure. In addition, it is well-known that age older than 65 years, history of serious bleeding, liver disease, ethanol abuse and reduced platelet count are significant risk factors for bleeding under anticoagulant therapy [27]. Therefore, a careful evaluation of patient must be taken into account when anticoagulation and thrombolytic agents are proposed for the treatment of thrombotic complications of cirrhosis, because the expected rate of severe bleeding complications seems higher than in the population usually treated with thrombolytics.

In conclusion, from our small series of three consecutive patients receiving locally delivered thrombolysis for TIPS thrombosis, we suggest that such approach is safe and efficient, but the risk of crippling rate of bleeding complications in high-risk cirrhotic patients must be strongly kept in mind (Table 1).

**Conflict of interest statement**

The authors have not declared any conflict of interest.

**References**


<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical and biological characteristics of patients at the time of thrombolysis.</th>
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<tr>
<td>Age (years)</td>
<td>47</td>
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<tr>
<td>Gender (M/F)</td>
<td>F</td>
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<tr>
<td>Delay between TIPS insertion and thrombolysis</td>
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<td>Serum bilirubin (μmol/l)</td>
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<td>Serum albumin (g/l)</td>
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<td>Prothrombin activity (%)</td>
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<td>γgl activity (IU/l)</td>
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<td>MELD score</td>
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TIPS: transjugular intrahepatic portosystemic shunt; M: male; F: female.
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