Thrombolysis for Non-malignant Portal Vein Thrombosis

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Abstract

Portal vein thrombosis (PVT) is thrombosis of the portal circulation. PVT is an uncommon thrombotic condition in the general population; on the other hand, it is one of the most common vascular disorders of the liver especially among patients with underlying chronic liver diseases, malignancy, and hypercoagulable states. The natural history and clinical outcome of PVT differentiate according to the site and extension of the obstruction in the portal venous system. Causes of PVT are cirrhosis, hepatobiliary malignancy, inflammatory conditions and inherited/acquired thrombophilia. Diagnosis of PVT is made by Doppler ultrasonography as the first-line choice. Treatment modalities range from conservative management to anticoagulation, thrombolysis, and thrombectomy. The primary end point was portal vein recanalization. In this section, we describe thrombolysis for non-malignant PVT.

Keywords

Portal vein · Thrombosis · Malignant · Thrombolysis · Thromboembolism Cirrhosis

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8.1 Introduction

Portal vein thrombosis (PVT) is partial or complete blood clot formation of the portal circulation. Thrombosis can extend to the portal branches to the splenic and/or the mesenteric veins. Clinical features differentiate according to the site and extension of the obstruction in the portal venous system [1, 2]. In partial obstruction, asymptomatic presentation and incidental diagnosis during routine workup is common [3]. Number of incidental PVT increases with use of abdominal imaging for other purposes [4]. If complete thrombosis occurs, it can lead to hepatic decompensation, variceal bleeding and intestinal infarction as a consequence of portal hypertension [5]. It is also divided into acute, subacute and chronic. Making this distinction is important in determining the approach to treatment [6, 7]. There are two different views in the acute/chronic distinction. Even though this is not a generally accepted definition, according to some clinicians, PVT was considered to be acute, if symptoms develop within 60 days prior to diagnosis [8, 9]. In fact, some other authors describe acute PVT as symptoms occurring within 7 days prior to diagnosis and subacute PVT if symptoms last longer than 7 days [10, 11]. Actually, acute and chronic PVT are different stages of the same disease [2]. Chronic stage definition is used when portal hypertension symptoms (collaterals/varices, ascites and splenomegaly) and portal cavernoma (formation of collateral vasculature bypassing the area of obstruction) occur [12].

8.1.1 Epidemiology

PVT was first described in 1868 by Balfour and Stewart in a 20-year-old patient with ascites, splenomegaly and esophageal varices [13]. Since then, it is a rare clinical diagnosis and the incidence of PVT is unknown. In general population, prevalence is 0.7 to 1/100,000 [14]. In certain conditions, such as cirrhosis, prevalence increases. There is a connection between the prevalence of PVT and the severity of liver disease. In compensated cirrhosis, estimated prevalence is less than 1%, meanwhile it is 8–25% in liver transplant candidates [15, 16]. According to the Sweden based study that was performed from 1970 to 1982 with 24,000 autopsies, the prevalence of PVT was 1%. This study revealed that the most common causes for PVT were cirrhosis (28%), primary or secondary hepatobiliary malignancy (23–44%), major infectious or inflammatory abdominal disease (10%), or a myeloproliferative disorder (3%). Predisposing factor was not found in 14% [17].

8.1.2 Pathophysiology and Etiology

PVT pathophysiology is similar to thrombus formation in any other vessel. In order to understand pathophysiology, Virchow's triad (endothelial damage, stasis and hypercoagulability) must be known [4, 5]. Pathophysiology changes according to the underlying etiology. Etiology of PVT can be divided into local and systemic (Table 8.1).

Table 8.1 Causes of portal vein thrombosis [4, 15, 18]

A. Local causes	*Cirrhosis*
	Malignancy
	• Hepatocellular carcinoma
	• Hepatobiliary cancer
	• Pancreatic cancer
	• Gastrointestinal cancer
	• Lymphoma
	Direct injury to portal vein
	• Surgery
	• Trauma
	• Shunts
	Inflammatory conditions
	• Pancreatitis
	• Cholecysititis
	• Diverticulitis
	• Inflammatory bowel disease
	• Connective tissue disease
	• Appendicitis and any other intra-abdominal infection
B. Systemic causes	*Inherited thrombophilia*
	• Factor V Leiden mutation
	• Protein C, S and antithrombin 3 deficiency
	• Prothrombin gene mutation
	Acquired thrombophilia
	• Myeloproliferative disorders: JAK 2 gene mutation, polycythemia vera, essential thrombocythemia, myelofibrosis
	• Paroxysmal nocturnal hemoglobinuria
	• Antiphospholipid antibody syndrome
	• Hyperhomocysteinemia
	• Pregnancy
	• Hormonal treatments

8.1.3 Clinical Presentation

PVT has a wide clinical presentation ranging from asymptomatic and incidental diagnosis, to mild to moderate abdominal pain, nausea, vomiting, to mesenteric ischemic symptoms with severe abdominal pain, hypotension, and even death [15]. Symptoms vary depending on many factors (acute/subacute/chronic; occlusive/non-occlusive; benign/malignant; and intrahepatic/extrahepatic).

In acute stage of PVT, if occlusion is partial, thrombus may be asymptomatic or may be associated with nonspecific symptoms, such as colicky pain, loss of appetite, nausea and vomiting [4, 19]. On the other hand, if occlusion is complete, it may present as acute or long-standing abdominal pain, signs of decompensated chronic liver disease (variceal bleeding, ascites, and hepatic encephalopathy), occult blood in stool, peritonitis, portal cholangiopathy, and intestinal ischemia. Sudden

worsening of the cirrhotic patient's clinic should suggest PVT development. When the extension of thrombosis reaches to the superior mesenteric vein (SMV) and mesenteric arches, life-threatening intestinal infarction risk could appear. Occlusion may extend into the splenic vein [18].

When acute PVT resolution fails, chronic PVT occurs. As a result, cavernous transformation develops [1]. Cavernous formation of portal vein (portal cavernoma) occurs between 6–20 days after unresolved PVT, and for the reason that portal vein flow stasis in cirrhosis usually prevents collateral dilatation, cavernomas are more common in patient without concomitant liver disease [5, 20]. Chronic PVT can lead to esophageal varices with bleeding, splenomegaly and ascites as a result of portal hypertension [15]. Endoscopic screening for gastro-oesophageal varices must be done within few months since varices may be seen as early as 1 month after acute PVT. If varices are not detected, endoscopic screening should be repeated 6 months later, if PVT recanalization has not been achieved [2].

8.1.4 Diagnosis of PVT

There are no specific laboratory tests to indicate PVT. Imaging methods are used in the diagnosis of PVT. In fact, PVT is an incidental finding in the majority of patients with cirrhosis. Doppler ultrasound (US) is the first-line technique for PVT diagnosis [18]. Doppler US is used commonly in screening cirrhotic patients for hepatocellular carcinoma (HCC) [21]. Contrast-enhanced imaging techniques, including contrast-enhanced ultrasound (CEUS) and contrast-enhanced computed tomography (CECT), are useful for diagnosis with higher sensitivity, allowing further characterization of PVT. These techniques allow a better definition of PVT extension and evaluation of underlying malignancy [5, 19, 22, 23]. Visualization of the entire mesenteric venous system and wide availability are advantages of a CT scan. On the other hand, risk of contrast nephropathy, radiation exposure, and technical variations should be considered. In the arterial phase of CECT and magnetic resonance imaging (MRI), intra-thrombus vascularity has been reported to be specific for malignant PVT [18, 24–28].

8.1.5 Management

Treatment of the underlying etiology of PVT is essential. For example, in the management of septic portal phlebitis, antibiotherapy and drainage of the abscess should be performed as soon as possible [3]. The primary goal of treatment is to promote portal vein recanalization and to prevent propagation of the thrombus [6, 21, 22]. Recanalization will prevent the complications of portal hypertension and mesenteric ischemia [4].

Treatment should be patient-specific and a delicate balance between thrombosis and bleeding should be maintained. The treatment of PVT ranges from close monitoring without intervention to anticoagulation, thrombolysis, thrombectomy, and

transjugular intrahepatic portosystemic shunt (TIPS). The clinician should make treatment decisions considering the involvement of other splanchnic veins, hypercoagulable states, local factors (infections, inflammatory disorders, and cirrhosis), malignancy, bleeding risk, and gastroesophageal varices [15]. Therapeutic decisions strongly depend on the etiology. When forming a treatment strategy, patients are considered in three main groups: patients with liver cirrhosis, with malignancies, and those unrelated to cirrhosis or malignancies [12]. In general, the primary treatment for acute/subacute PVT is immediate systemic anticoagulation [29, 30].

In this section, we will focus on thrombolysis for non-malignant PVT. The use of intravascular thrombolytic agents originates back to the 1960s with the pulmonary embolism treatment. By the 1970s, catheter-directed thrombolysis for vascular occlusion entered the mainstream. Nowadays, thrombolytics are used in many thrombotic conditions, including acute peripheral/visceral arterial occlusion, coronary artery thrombosis, thrombosed dialysis grafts, thrombosed intravascular catheters and deep vein thrombosis. Until now, urokinase, streptokinase, alteplase, reteplase, and anistreplase have been used as thrombolytic agents. Each of them converts plasminogen to plasmin, which then degrades fibrin and fibrinogen to their fragments and in this way accelerates lysis of thrombus. These agents have been used with or without anticoagulants, platelet-receptor antagonists, and plasminogen or thrombin inhibitors. For more efficient treatment, thrombolytic agents can be given directly into the thrombus, thus a high local drug concentration is achieved [31].

8.2 Thrombolysis

The goals of the treatment are complete recanalization of portal vein to prevent further extension of thrombus into the mesenteric veins and prevent further morbidities caused by chronic PVT [6, 32].

Current treatment options of PVT vary from a conservative approach as monitoring with no treatment to anticoagulation, thrombolysis therapy, replacement of TIPS, and surgical thrombectomy [33]. Spontaneous resolution of obstruction is extremely rare with conservative approach and higher incidences of portal hypertension associated morbidities are reported. Within acute settings, short-term complications, like bowel infarction and sepsis, can occur, and even could result in mortality [6, 33].

Suitable conditions for using thrombolysis are if the patient has intensifying abdominal pain due to extension of thrombus under anticoagulation therapy or if the risk of intestinal necrosis and infarction is high (mostly seen with multiple vessel involvement) [15].

Although there is no consensus on the initiation time of thrombolysis from the diagnosis, early detection of thrombus and initiation of treatment could possibly give benefit of increasing success due to less organized thrombus at the beginning. In a systematic review study, the interval from the initiation of the symptoms to beginning of the treatment was from up to 4–60 days [6, 31, 34, 35]. Longer intervals from diagnosis to recanalization could increase the risk of long-term

complications. In a 2-year follow up study, after 6 months of treatment, no obvious benefit of anticoagulation is observed on recanalization. If treatment delays after the second week of symptoms onset, recanalization rates are as low as 69% to 25% [4, 36, 37].

Total venous occlusion and portal hypertension at the time of diagnosis lowers the chance of recanalization [38]. Especially in cavernous transformation of PV, the possibility of recanalization is lower in chronic PVT patients [39].

Even though using systemic thrombolysis as an alternative to anticoagulation is related to higher percentages of recanalization, there is still an increased risk of hemorrhagic complications [40, 41]. Decisions on treatment options should be made on an individual basis upon a multidisciplinary approach.

8.2.1 Contraindications

Selecting patients for thrombolysis treatment with PVT, clinician should assess contraindications before the intervention, such as recent stroke, presence of CNS tumor, active bleeding, known bleeding diathesis, former ischemia with bleeding or CNS surgery in 4 weeks, major surgery in 2 week or CNS hemorrhage within 12 months prior, known allergic reaction to thrombolytic materials, platelet count lower than 50×10^9/L or fibrinogen level under 1 g/L [3, 38].

Treatment aims at achieving recanalization of the thrombosed vessel, so restoring flow and preventing the onset of early and late complications related to thrombosis progression and portal hypertension.

The recanalization rate is even lower in patients with chronic PVT, in particular in those with cavernous transformation of the portal vein.

8.2.2 Treatment Protocols

European Association for the Study of Liver (EASL) suggests that without any contraindications current first-line treatment of acute symptomatic PVT depends on anticoagulants like unfractionated (UFH) or low molecular weight heparin (LMWH) [22].

In case of asymptomatic patients without underlying malignancy, hypercoagulability or thrombus extension to mesenteric vessels, monitoring without treatment is suggested [4]. However, if the patient has intensifying abdominal pain due to extension of thrombus under anticoagulation or if the risk of intestinal necrosis and infarction is high, commonly used methods are either systemic thrombolytic therapy via central venous catheter or catheter-directed local approaches, such as chemical, mechanical thrombolysis like suction or agitation, balloon angioplasty and stenting [3, 15].

Mechanical thrombectomy can be used in patients with contraindications to thrombolytic treatment or if the clinician prefers to reduce the dose of thrombolytics

in favor of the patient's current situation. In the acute stage of clot formation, thrombus is more fragile and it can be fragmented by agitation which increases the effect of thrombolytics to dissolve thrombus. For this modality, pigtail catheters, balloon or other special devices could be used [32]. Also, among mechanical thrombectomy modalities, rheolytic thrombolysis is reported to have an easy practice and related to lesser complications and shorter hospitalization time. Rheolytic thrombolysis is practiced as saline jet infusion to break down the clot [33, 40, 42]. Pulmonary emboli from fragmented clot, restenosis, and disruption of vessel wall integrity are complications of this procedure [43, 44].

Surgical thrombectomy and resection are preferred, if there is suspected intestinal necrosis, perforation or peritonitis. Though it has a risk of surgical complications, such as short bowel syndrome, in terms of mortality, 2-year survival rate or recurrence, no difference has been shown between non-surgical and surgical approaches [45].

8.2.3 Systemic Thrombolysis

For systemic thrombolysis, a recombinant human tissue-type plasminogen activator (tPA) or urokinase could be used as thrombolytic agent. Compared to urokinase, tPA is more expensive but has a higher affinity for fibrin molecule. Immediately after attachment, tPA converts plasminogen to plasmin thus induces disintegration of clot [38, 46].

After ruling out contraindications and getting consent, IV infusion of urokinase or tPA is initiated from a central venous line. Preferred tPA dose is 0.05 mg/kg/h up to a maximum dose of 4 mg/kg. Preferred urokinase dose is 400,000-600,000 U/day [46]. Heparin is also administered at a maintenance dose of 500-1000 IU/h. Thrombolysis infusion time varies between institutional practices from a few hours to 7 days on average. During infusion follow up, imaging is made between 48–72 h by appropriate imaging methods [38].

If abdominal pain does not ameliorate during the next 48–72 h and imaging evidences suggest no improvement on recanalization, catheter directed local thrombolysis options should be revised.

8.2.4 Catheter Directed Local Thrombolysis

Catheter directed local thrombolysis is used after failure with systemic approach or when the patient has any contraindication to systemic approach.

Transhepatic approach is preferred for non-cirrhotic patients with acute or subacute PVT. It is an easy procedure with lower cost compared to other methods, but carries a greater risk for hemorrhage during thrombolysis. Herein, we would like to present a case with symptomatic acute PVT due to major abdominal surgery successfully treated by catheter directed thrombolysis, as follows.

A 34-year-old male patient with no previous chronic disease history presented to the emergency department on April 19, 2020 with complaints of abdominal pain, nausea and vomiting. Abdominal CT imaging was performed with a diagnosis of acute abdomen. The size of the liver was normal, and its contours were smooth. The spleen was normal in size and its parenchyma was homogeneous. The appearance compatible with dilated appendix was measured 10 mm and it was evaluated in favor of acute appendicitis due to the presence of significant inflammation around it. Laparoscopic appendectomy was performed.

Three weeks after the operation, the patient returned to the emergency room due to the acute abdominal pain again. His blood pressure was 120/80 mmHg and heart rate 84 beats per min. His general condition was good, conscious and cooperative. Hepatomegaly was absent. Other systems were normal. His uncle's daughter had a history of thrombus. Laboratory examinations showed that whole blood count was normal. C-reactive protein was 105 mg/L (normal: 0–5), INR: 1.07, APTT: 41.8 s, blood urea: 42 mg/dL, creatinine: 0.8 mg/dL, Na: 142 mmol/L, potassium: 4.1 mmol/L, AST: 34 U/L, and ALT: 106 U/L. Abdominal contrast CT revealed that liver size was normal with smooth contour and normal size of the pancreas and spleen and a physiological calibration at abdominal aorta. The intrahepatic branches of the portal vein were entirely thrombosed and its extrahepatic segment was nearly totally thrombosed. The thrombus has been extended to the distal branches of SMV (Fig. 8.1a, b).

Final diagnosis was SMV thrombosis and acute thrombus in the portal vein. Thrombolytic therapy was planned due to acute abdominal pain, acute thrombus appearance, and the young age of the patient. Interventional radiology was performed. A 21G needle accompanied by ultrasound was entered into the right portal vein (Fig. 8.1c, d). A hydrophilic guide wire was placed. A 20 cm long infusion catheter was placed in the SMV. On the first day, it was decided to give tPA *(alteplase)* at a dose of 2 mL/h infusion and heparin 800 IU/h infusion and aPTT was followed. It was planned to perform control portography after 20 h. The general condition of the patient was good, conscious and cooperative during the whole procedure.

Splenoportography performed at the 20th hour of treatment revealed no complete patency in the SMV and portal vein. The patient did not have any complaints of pain. On the second day of treatment, tPA (alteplase) 1 mL/h infusion and heparin 1500 U/h infusion were continued. An angiography performed on the third day of treatment showed that portal vein lumen was open (Fig. 8.1e). On the fourth day of treatment, tPA infusion treatment was discontinued and heparin was continued at 1500 U/h. The general condition of the patient was good. With the aim of advanced examination, evaluation and treatment, antithrombin III, protein C and protein S levels were requested to eliminate the conditions that may cause PVT. No significant coagulating pathological condition was detected. Then, LMWH was started while heparin was stopped. On the seventh day of treatment, LMWH was stopped and an oral anticoagulant (rivaroxaban) treatment was started and the patient was discharged to home.

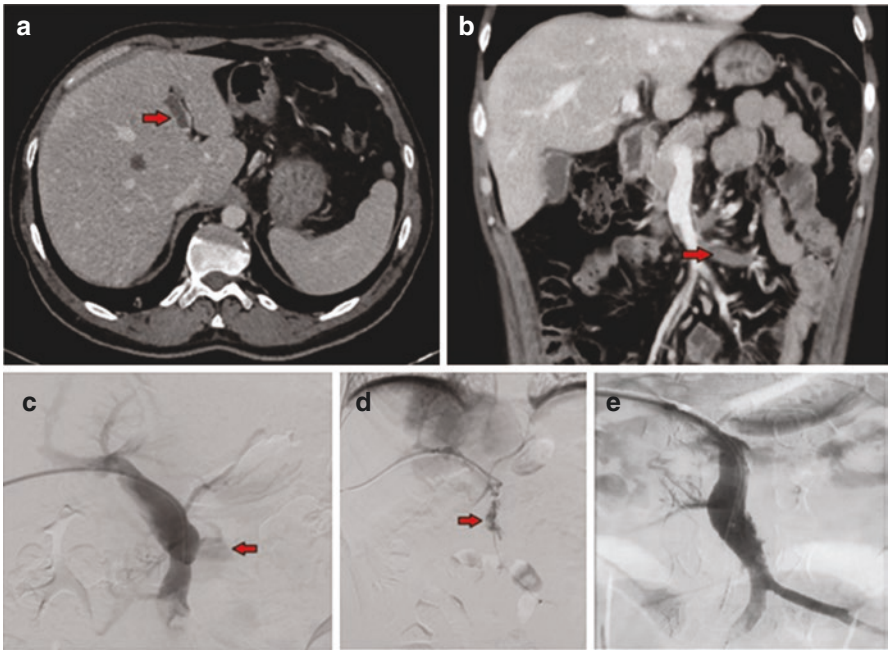

Fig. 8.1 A case with acute PVT successfully treated by catheter directed thrombolysis. (**a**, **b**) Abdominal contrast CT revealed that the intrahepatic branches of the portal vein were entirely thrombosed and its extrahepatic segment was nearly totally thrombosed. The thrombus has been extended to the distal branches of SMV (red arrow). (**c**, **d**) A 21G needle accompanied by ultrasound was entered into the right portal vein at interventional radiology. A hydrophilic guide wire was placed. A 20 cm long infusion catheter was placed in the SMV for therapeutic purpose. Splenoportography performed at the 20th hour of treatment revealed no complete patency in the SMV and portal vein. (**e**) On the third day of treatment, splenoportography showed that portal vein lumen was open

At the third month follow-up, he has no complaints, and a Doppler ultrasonography demonstrated the main portal vein diameter of 13.2 mm with mild sequelae intimal thickening, and patent portal vein and its branches, SMV and splenic vein lumens. No major recurrent thrombosis was detected. FibroScan elastography showed that median liver stiffness value was 5.6 kPa (IQR/med: 4%), suggesting F0-F1 fibrosis (no significant liver injury).

Transileocolic approach is preferred in patients with failed TIPS or PVT patients with ascites, but has less hemorrhagic risk and requires surgical intervention.

Transjugular approach requires portal venous access via inferior vena cava or hepatic veins and may be used to create a TIPS, and it has a lower risk of bleeding complication [31, 40].

Indirect approach is used in case of portal vein anatomical variations, with administration of thrombolysis to SMA via femoral artery or radial artery, and considered to be a effective and safer approach, compared to systemic thrombolysis hence being less invasive [3, 34].

8.2.5 Follow Up During Treatment

During the treatment, the patient should be evaluated for symptom improvement. Periodic complete blood count along with prothrombin time, aPTT, INR, fibrinogen, blood urea, electrolytes, and liver enzymes should be monitored every 6–12 h [38]. If fibrinogen levels drop under 1 g/L, infusion must be ceased. Before the intervention, if aPTT levels are not in a normal range, heparin infusion must be monitored with anti-Xa targeting the level 0.5–0.8 IU/mL during the infusion. Especially with UFH use, heparin induced thrombocytopenia is a life-threatening situation with falling of platelet counts over 50%, and after cessation of heparin, platelet count comes back to normal range [4, 22]. Clinicians also must be vigilant in terms of local or intracranial hemorrhages during treatment.

8.2.6 Acute and Chronic Complications

In acute stage, minor local or systemic bleeding, allergy, vessel injury, need for surgical intervention, sepsis and rarely death have been reported [6, 47].

One of the significant complications of PVT treatment is extrahepatic portal hypertension as recognized with elevation of portal venous pressure above 12 mmHg at rest. For recognizing portal hypertension with the help of clinical signs and imaging manifestations, ascites, variceal bleeding, hypersplenism and related thrombocytopenia, and hepatic encephalopathy should not be overlooked [2, 48].

8.2.7 Long Term Prognosis

Recently, survival rates are improved on account of early diagnosis and starting early anticoagulation also with new invasive approaches. Even incomplete recanalization affects prognosis positively.

Without former liver disease for acute PVT, 5-year mortality rate is up to 15%, which is mostly related to underlying disease or complications after intervention [49]. For chronic PVT, mortality for 5 years is as low as 5–10%, which is mostly related to age, underlying diseases, and etiology of PVT, rather than PVT complications [2, 50].

8.2.8 Further Imaging and Medical Follow Up

After successful treatment, the complaints of the patients are expected to decline within 2 weeks. Periodic outpatient controls should be done for signs of portal hypertension in further follow-up. If the patient has no complaints or signs of restenosis, checking for recanalization with doppler US at 3 and 6 months is sufficient. CT or MRI is suggested if the patient has signs of ischemic intestinal damage. Repeated imaging at 3 weeks is reported [2, 6, 51]. After acute PVT, if complete

patency is not achieved, endoscopic evaluation for gastroesophageal varices should be scheduled within few months and repeated 6 months following. Without sufficient evidence, further assessment with endoscopy is recommendable after 2–3 years [2, 52]. For patients with gastroesophageal variceal bleeding, prevention is provided with the use of beta blockers or endoscopic band ligation [22].

Anticoagulation treatment decision should be made considering the patient's further risk of bleeding and evaluation of each case must be made on an individual basis. On discharge, transition to warfarin after initial administration of LMWH is recommended. If the patient has JAK2 mutation, daily acetylsalicylic acid use is recommended [38].

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