

Systemic Thrombolysis of Acute Portal Venous System Thrombosis in Patients with Liver Cirrhosis: A Pilot Study



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Abstract:

Background: The prevalence of Portal Vein Thrombosis (PVT) is highly variable at different stages of liver disease: in compensated patients 10%, in decompensated patients 17%, in acute decompensated cirrhosis 9%, and in post-liver transplantation patients 2-26%.

Aim: The aim of the study was to assess the efficacy and safety of systemic thrombolysis in acute portal vein thrombosis in patients with liver cirrhosis.

Methods: A total of 10 compensated cirrhotic patients with acute portal vein thrombosis were examined by abdominal ultrasonography with color Doppler and Contrast-enhanced computerized tomography. Continuous intravenous infusion of recombinant tissue plasminogen activator (r-tPA) and Low molecular weight heparin (LMWH) was used to treat all patients for a maximum of 7 days. Patients were followed up for improvement of clinical symptoms and radiological by abdominal ultrasound with color Doppler and contrast-enhanced computerized tomography.

Results: The regimen of therapy was found to be well-tolerated by all the patients. At the end of the seven days, six patients (60%) had full recanalization of the portal vein, while three had partial recanalization (30%) and no recanalization in only one patient (10%).

Conclusion: The preliminary data indicate that systemic thrombolytic therapy combined with low molecular weight heparin for the treatment of PVT appears to be safe and effective over a few days with no clinically significant side effects.

Keywords: Liver cirrhosis, Acute portal vein thrombosis, Systemic thrombolytic therapy, Liver transplantation, PVT, MV.

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Cite as: Soliman S, Ismail A, Badawi R, Elkhawany W. Systemic Thrombolysis of Acute Portal Venous System Thrombosis in Patients with Liver Cirrhosis: A Pilot Study. Open Biomark J, 2024; 14: e18753183285252. <http://dx.doi.org/10.2174/0118753183285252240329035743>



Received: November 01, 2023

Revised: February 25, 2024

Accepted: February 27, 2024

Published: April 24, 2024



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1. INTRODUCTION

Portal Vein Thrombosis (PVT) is described as partial or total obstruction of the main portal trunk by a thrombus, which might potentially include the right and / left intrahepatic portal branches. In addition, PVT can spread to the mesenteric vein (MV) and splenic vein, resulting in

portal venous thrombosis. Although this is not a widely recognised criterion, certain authors consider PVT to be acute if symptoms appear within 60 days after diagnosis [1, 2]. Others describe acute PVT as symptoms occurring within 7 days after diagnosis and subacute PVT as symptoms lasting more than 7 days [3, 4]. Typically, Signs

of portal hypertension include cavernous changes in the portal vein (PV), the formation of collaterals or varices, and significant splenomegaly are used to differentiate acute PVT from chronic PVT. The prevalence of PVT varies greatly depending on the stage of liver disease: 10% in compensated patients, 17% in decompensated patients, 9% in acute decompensated cirrhosis, and 2-26% in post-liver transplantation patients [5-7]. A recent study found a PVT prevalence of 17.2% in cirrhotic patients, with a higher prevalence of acute PVT (15%) than chronic PVT (2.2%) [8]. Acute PVT or mesenteric vein thrombosis (MVT) is frequently difficult to diagnose clinically. Patients may be asymptomatic or suffer generalized abdominal pain.

In certain circumstances, PVT or MVT is discovered by chance while imaging for an abdominal pain workup. On the other hand, patients may have gastrointestinal tract bleeding, severe abdominal pain, diarrhea, and vomiting. When the PVT spreads to the mesenteric or splenic veins, an acute abdomen with bowel congestion, signs associated with mesenteric ischemia, and sepsis features such as shock or multi-organ failure can appear. Acute PVT may manifest as acute decompensation in patients with liver cirrhosis [9]. Adriano De Santis and colleagues showed that thrombolytic treatment of acute PVT in patients with cirrhosis with intravenous recombinant tissue plasminogen activator (r-tPA) and Low molecular weight heparin (LMWH). It seems to be safe and effective, and it can greatly lower esophageal varices pressure [10].

The aim of the study was to evaluate the effectiveness and safety of systemic thrombolysis in patients with liver cirrhosis who had an acute PVT.

2. PATIENTS AND METHODS

This study is a prospective pilot study that includes 10 cirrhotic patients complaining of an acute PVT admitted to the Department of Tropical Medicine & Infectious Diseases and the Department of Vascular Surgery, Tanta University Hospital, in the period between December 2022 and August 2023. Inclusion Criteria: This study included cirrhotic patients with an acute PVT diagnosed by abdominal ultrasound with pulsed, color Doppler, and Contrast-enhanced computerized tomography.

Criteria for exclusion: Patients with persistent PVT who did not exhibit portal carcinomatosis were excluded. We also excluded patients having any contraindications for thrombolytic therapy as the age above 70 years, recent surgery within 30 days, recent cerebral infarction or intracranial hemorrhage, active bleeding, severe uncontrolled hypertension, active malignancy as hepatocellular carcinoma (HCC). Pregnant and lactating women were also excluded. Initial Assessment: A thorough medical history was taken with special attention to any prior upper endoscopy, surgical procedures, splenectomy, and bleeding history. A detailed clinical examination was performed to check for ascites, splenomegaly, and jaundice, which are manifestations of portal hypertension.

Laboratory investigations, included complete blood picture (CBC), liver function tests, prothrombin time,

activated partial thromboplastin time (APTT) and international normalized ratio (INR), D dimer, kidney function tests, serum α -fetoprotein, and hepatitis B and C viral markers. Imaging tests included a color Doppler portal vein examination and abdominal ultrasonography to diagnose liver cirrhosis. Contrast-enhanced computerized tomography was performed to exclude HCC and confirm the diagnosis and extent of the thrombus to the mesenteric, splenic, and portal vein and its branches. Upper endoscopy was performed to evaluate the presence, grades, and risky signs of esophageal varices. Prophylactic band ligation of varices was performed before starting any treatment. Cirrhosis was diagnosed on the basis of clinical, laboratory, and imaging studies, and the Child-Pugh score was determined.

Plan of therapy: In cases of acute PVT presenting with pictures of the superior mesenteric vein occlusion with edema in the bowel wall with the potential risk of developing subsequent mesenteric arterial occlusion, systemic thrombolysis was immediately started in combination with low molecular weight heparin. In cases of acute PVT receiving treatment with low molecular weight heparin and not showing any clinical improvement within 7 days, systemic thrombolytic therapy was given. The presence of persistent vomiting and unresolved abdominal pain were the main signs of non-improvement after initial therapy with low molecular weight heparin alone.

Dosage and duration of therapy: Continuous intravenous infusion of r-tPA and LMWH was used to treat all patients for a maximum of 7 days, r-tPA. Actilyse® 50 mg, (Boehringer Ingelheim) was given out by intravenous continuous infusion with a dose of 0.25 mg/kg/day. Subcutaneous administration of LMWH was done based on body weight (BW): 60 mg BID. Of Enoxaparin (Clexane, Sanofi Aventis) for a weight between 60 and 79 kilograms, 80 mg BID of Enoxaparin for a BW between 80 and 99 kilograms.

Follow up: Patients were followed up by improvement of clinical symptoms and radiological by abdominal ultrasound with color Doppler, which was performed every 2 days and confirmed by contrast-enhanced computerized tomography after 7 days of systemic thrombolysis. Follow up of laboratory parameters (CBC, INR, D-dimer, liver enzymes) after 2 days of treatment and at the end of treatment. Long-term anticoagulation therapy was maintained for 6 months. Written informed consent was obtained from all patients, and the study was approved by the ethical committee of Tanta University's faculty of medicine. Approval code of ethical committee 36162/12/22.

Statistical analysis: Data analysis was performed using SPSS version 20 (Statistical Package for Social Science) for Windows (IBM Corp., Armonk, N.Y., USA). Quantitative data were presented as mean and standard deviation (SD). Qualitative data was presented in the form of numbers and percentages. P value was calculated as either non-significant if > 0.05 , significant if ≤ 0.05 , or highly substantial if < 0.001 .

3. RESULTS

Fifteen patients with an acute PVT in cirrhotic patients were recruited for the study; five were excluded, three because of HCC, and 2 because of a recent splenectomy. Therefore, only 10 patients were enrolled from the departments of Tropical Medicine & Infectious diseases and Vascular Surgery, Tanta University hospital. The age of the patients ranged from 45 to 63 (52 ± 10.8); seven of them were males and 3 were females. All patients presented with abdominal pain, five patients had a fever, and six patients suffered from vomiting. The Child-Pugh score was evaluated, and four patients were found to be Child A and 6 patients were Child B. Basic demographic and clinical data of the patients are shown in Table 1. The site of the thrombus was found in the main portal vein in all patients, in the right branch of the portal vein in 5 patients (50%), in the left branch in 3 patients (30%), in superior mesenteric vein in 5 patients (50%) and splenic

vein in 3 patients (30%) as shown in Table 2. Five cases (50%) with acute PVT presented with superior mesenteric vein occlusion and edema in the bowel wall with the potential risk of developing subsequent mesenteric arterial occlusion; systemic thrombolysis was immediately started in combination with (LMWH). The onset of clinical presentation ranged between 7 to 20 days before initiation of the protocol of therapy. Five patients (50%) with acute PVT were treated with LMWH and did not show any clinical improvement within 7 days, and systemic thrombolytic therapy was given. The combination of (r-tPA) with (LMWH) was used for all patients. Monitoring for clinical improvement of the symptoms and signs of PVT was maintained throughout the duration of therapy. In addition, laboratory follow-up was performed for D dimer, INR, liver enzymes, renal function tests, platelet count, white blood cell count, and hemoglobin, as shown in Table 3. At the end of treatment, abdominal pain resolved in

Table 1. Demographic data and clinical presentation of the patients.

Parameter	Number (10 Patients)	%
Male	7	70
Female	3	30
Age (in years)	52 ± 10.8	
Clinical presentation:	-	-
Fever	5	50
Abdominal Pain	10	100
Vomiting	6	60
Onset of clinical presentation (in days)	7-20 days	
Child-Pugh Score	-	-
Child A	4	40
Child B	6	60
Child C	0	0

Table 2. Baseline radiological data regarding site of portal venous system thrombus.

Site of Thrombus	Number	%
Main Portal Vein	10	100
left portal vein branch	3	30
Right Portal vein branch	5	50
Superior Mesenteric Vein	5	50
Splenic Vein	3	30

Table 3. Laboratory investigations of the patients before and after therapy.

Lab Parameter	Base Line	After 2 d	After 1w	P value
Hemoglobin	10.1 ± 1.2	10 ± 1.3	9.9 ± 1.4	0.12
Platelet count ($\times 10^3$)	105 ± 23	102 ± 18	99 ± 21	0.24
White blood cells ($\times 10^3$)	11 ± 3	10 ± 2.5	9.8 ± 1.4	0.53
INR	1.4 ± 0.2	1.5 ± 0.2	1.4 ± 0.3	0.67
AST	75 ± 14	73 ± 16	65 ± 12	0.43
ALT	69 ± 11	67 ± 10	59 ± 9	0.86
D dimer (mg/L)	0.8 ± 0.3	0.7 ± 0.35	0.6 ± 0.2	0.16

Abbreviations: INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; significant $P \leq 0.05$.

Table 4. Radiological data at the end of therapy.

	Number	%
Complete recanalization	6	60
Partial recanalization	3	30
No recanalization	1	10

90% of patients, and fever and vomiting completely disappeared. All the patients using the above-mentioned doses found the regimen of therapy to be well tolerated. Only one patient developed a small conjunctival hemorrhage, which was self-limiting and improved after 2 weeks. This patient was hypertensive but controlled on anti-hypertensive medications. No other adverse effects or significant laboratory derangements were encountered during the duration of therapy. At the end of the seven days, six patients (60%) had full recanalization of the portal vein, while three had partial recanalization (30%) and no recanalization in only one patient (10%) as shown in Table 4. Regarding the five patients with superior mesenteric vein thrombosis, two of them improved clinically after 24 hours, and the remaining three patients enhanced after 48 hours after initiation of therapy.

4. DISCUSSION

Cirrhotic individuals are hypercoagulable, as evidenced by normal or elevated thrombin levels resulting from disrupted hemostatic equilibrium. Anticoagulation factors like antithrombin and protein C are lower in these individuals, whereas procoagulation factors like factor VIII and von Willebrand (vWF) are elevated.

Although thrombocytopenia is common, the thrombogenic potential of the platelets is elevated due to reduced vWF cleaving protease ADAMTS-13 activity, resulting in altered vWF-platelet interaction. Endotoxemia is caused by bacterial translocation from the intestinal mucosa to the portal vein, which is common in cirrhotic patients and also causes a prothrombotic condition [11-13].

Without definitive recommendations, the appropriate therapy for PVT in cirrhosis remains unknown. Anticoagulation appears to be the first-line therapy of choice, aiming to avoid thrombus extension or recurrence, restore venous patency, and prevent thrombotic consequences such as portal hypertension and intestinal ischemia [14].

LMWH and direct oral anticoagulants are relatively safe and effective in patients with compensated liver cirrhosis and PVT. But the safety and efficacy of direct oral anticoagulants in cirrhotic patients with Child-Pugh C cirrhosis needs further evaluation [15]. In patients with cirrhosis and an acute or subacute non-tumoral PVT, the American Gastroenterological Association (AGA) Guideline suggests using anticoagulation over no anticoagulation for treatment of an acute PVT with putting the bleeding risk in consideration after anticoagulant use [16]. In the present study, 10 cirrhotic patients with acute PVST were treated with low dose r-tPA plus LMWH for seven days

and complete recanalization of portal venous system thrombosis (PVST) was achieved in 6 patients and partial recanalization in 3 patients and no recanalization in one patient. Similarly, nine cirrhotic patients with acute PVT were studied in Italy by De Santis *et al.* (2010). They used the same therapeutic regimen as our study. Complete clearance of thrombosis occurred in four patients, with partial resolution in four patients and no resolution in one patient [9]. Gao *et al.* in 2022 reported a case of 56-year-old man with acute PVT extending to splenic and superior mesenteric veins. He was not responding to LMWH after five days, so he was treated by systemic thrombolysis in addition to LMWH for seven days. He showed clinical improvement with recanalization of the thrombosed portal venous system [17]. On the other hand, Benmassaoud *et al.*, in 2019, recruited 22 patients with acute PVST, and all showed intestinal wall edema on presentation. Systemic thrombolysis was started, and clinical improvement was achieved for 45% of the patients, while 55% of them were not improved so they underwent TIPSS insertion for catheter-directed thrombolysis (CDT). At the end of therapy, clinical improvement was achieved in 91% of patients and recanalization in 86%. Only one patient required surgical exploration and resection of gangrenous small intestine [18]. Jiang *et al.*, 2017, published an RCS that included 40 patients with acute PVST, in 20 patients, catheter-directed thrombolysis through TIPS. In the other 20 patients, CDT was conducted via the superior mesenteric artery (SMA). Within forty-eight hours, the symptoms of all patients in both groups had improved. PVT was improved in Seventeen (85%) of the SMA group and Fourteen (70%) of the TIPS group. They concluded that both CDT approaches in treating acute PVST in cirrhotic patients are considered safe and effective [19]. Gao *et al.*, 2023 published a meta-analysis that initially found 2134 publications, 29 cohort studies, and 131 case reports or case series. According to the cohort studies. The total response to thrombolytic treatment was 93%, a complete recanalization was 58%, bleeding events during thrombolysis was 18%, additional bowel resection was required in 3%, recurrent thrombus was only 1%. Thirty-day mortality was 4%. The interval between onset of symptoms and initiation of thrombolysis ≤ 14 days was significantly associated with complete recanalization of PVST [11]. In the present study, systemic thrombolysis was used in combination with LMWH as a therapeutic approach for acute PVT, taking advantage of the short half-life of r-tPA that makes it very safe even in cirrhotic patients.

It acts only at the thrombus site by fibrinolysis and rapid restoration of the vessel patency, which is needed in certain situations when the time factor is crucial, as in

cases of SMV thrombosis with impending intestinal ischemia [10, 20].

CONCLUSION

The preliminary data indicate that systemic thrombolytic therapy combined with low molecular weight heparin for treating acute PVT appears to be safe and effective over a few days with no clinically significant side effects.

This study faced some limitations, as the small size of participants. Additionally, investigations for thrombophilic disorders couldn't be performed.

A larger sample-sized studies are recommended with a longer duration of follow-up.

LIST OF ABBREVIATIONS

PVT	=	Portal Vein Thrombosis
SMV	=	Superior Mesenteric Vein
MVT	=	Mesenteric Vein Thrombosis

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethical committee of Tanta University's faculty of medicine. Approval code of ethical committee 36162/12/22.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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