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Fondaparinux is effective for acute portal vein thrombosis in decompensated cirrhotic patients

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Abstract

Portal vein thrombosis (PVT) is a rare but serious complication in the decompensated stage of cirrhosis, and recurrent upper gastrointestinal bleeding and refractory ascites can occur in such patients. In decompensated cirrhotic patients, the application of conventional anticoagulant therapy is limited due to severe coagulation disorders, thrombocytopenia, and history of gastrointestinal bleeding.

In this study, we sought to investigate the effect of fondaparinux on acute PVT in decompensated cirrhotic patients.

Patients were treated with fondaparinux (2.5 mg, *q* 24 h, subcutaneously) in the region of the umbilicus for conventional liver protection, after a clear diagnosis was made and contraindications such as active bleeding were ruled out. Other anticoagulants and circulation-improving drugs were not administered. Platelet count, prothrombin time, international normalized ratio, D dimer (DD), and liver function were measured. Furthermore, portal vein color Doppler ultrasound was performed every 7 days while patients were treated with fondaparinux and after portal vein recanalization.

The portal vein was recanalized in all patients after treatment ($P = .018$). The decline in DD had a predictive value for portal vein recanalization ($P = .018$). No side effects such as bleeding or thrombocytopenia occurred in any of the patients ($P > .05$).

Selective factor Xa inhibitor fondaparinux is effective and safe for acute PVT in decompensated cirrhotic patients.

Abbreviations: DD = D dimer, DVT = deep vein thrombosis, HIT = heparin-induced thrombocytopenia, INR = international normalized ratio, PLT = platelet count, PT = prothrombin time, PVT = portal vein thrombosis.

Keywords: advanced cirrhosis, anticoagulation, fondaparinux, portal vein thrombosis, recanalization

1. Introduction

Portal vein thrombosis (PVT) is a rare but serious complication in the decompensated stage of cirrhosis, and recurrent upper gastrointestinal bleeding and refractory ascites can occur in such patients. Three large clinical studies reported that the incidence of deep vein thrombosis (DVT) in patients with cirrhosis was 0.5%, and one study found that the incidence of DVT was higher in cirrhotic patients than in noncirrhotic patients.[1] PVT is a manifestation of DVT, which can be classified into acute and chronic PVT, according to the onset of the disease. Specifically, if PVT symptoms occur within 60 days before admission, the condition is referred to as acute PVT.[2] Embolectomy, liver transplantation, and thrombolytic therapy are all effective therapeutic strategies. However, none of those procedures can be performed in patients with decompensated cirrhosis due to the presence of severe liver dysfunction, coagulation disorders, and bleeding tendencies. In patients with acute PVT, early anticoagulation treatment reportedly resulted in a higher recanalization rate of the portal vein.[3] The optimal anticoagulation regimen for the treatment of PVT has not been determined yet and no clear recommendations exist regarding this question in recent guidelines and consensus publications. The choice of anticoagulation regimen is particularly difficult in the cirrhotic individual, mostly because anticoagulation monitoring is complex in this particular situation.[4] In decompensated cirrhotic patients, the application of conventional anticoagulant therapy such as warfarin and low-molecular-weight heparin is limited due to severe coagulation disorders, thrombocytopenia, and history of gastrointestinal bleeding.

Factor Xa inhibitors exert its effects primarily via the specific inhibition of antithrombin on Xa. The recommended level of Xa inhibitors for the prevention of DVT has been published, and has been reported safe to use in patients with abnormal liver function.[5] Rivaroxaban, Edoxaban, and Apixaban are oral anticoagulant agents of factor Xa inhibitor class. They can be prescribed in a fixed dosage without coagulation monitoring. But the drug instructions of Rivaroxaban, Edoxaban, and Apixaban have made clear that they are contraindicated to use in the patients with coagulopathy and clinically relevant bleeding risk of liver disease, especially in the decompensated cirrhotic patients with Child–Pugh class of B or C. Fondaparinux is an indirect, selective, and reversible factor Xa inhibitor, which is used for the prevention of venous thromboembolic events and myocardial infarction. It is safe to use in patients with abnormal liver

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function. It can be used carefully in patients with prothrombin abnormally elevated refer to the instruction.[6] The efficacy and safety of fondaparinux have been examined in several Phase II and III clinical trials.[6,7] The aims of this study were to evaluate the selective Xa inhibitor fondaparinux in the treatment of acute PVT in 7 patients with decompensated cirrhosis, and to provide a brief review of the literature.

2. Methods

2.1. Subjects

From October 2014 to October 2015, patients diagnosed with decompensated cirrhosis were included into this study. Tumor thrombus was excluded and acute PVT was confirmed in these patients. Exclusion criteria were as follows: patients with cavernous transformation of the portal vein, active bleeding, bacterial endocarditis, and compensated cirrhosis. All patients were treated at the First Affiliated Hospital of Zhengzhou University. There are no current funding sources for this study. The details of the study were explained to the patients, and all patients provided a written informed consent. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University.

2.2. Clinical assessment

Platelet count (PLT), prothrombin time (PT), international normalized ratio (INR), D dimer (DD), and liver function were measured. Portal vein color Doppler ultrasound was performed every 7 days while patients were treated with fondaparinux and after patients underwent portal vein recanalization. These tests were performed using ACL-TOP automated coagulation analyzers and ancillary reagents (Beckman-Coulter, USA), LH750 hematology analyzers and ancillary reagents (Beckman-Coulter), Cobas8000 automatic biochemical immunoassay analyzer and ancillary reagents (Roche, Germany), and an Aloka α10 color Doppler ultrasound instrument (Japan).

2.3. Therapeutic intervention

Patients included into this study were administered with fondaparinux (2.5 mg, *q* 24 h, subcutaneously, the recommended dose by the drug instruction) in the region of the umbilicus for conventional liver protection, after a clear diagnosis was made and contraindications such as active bleeding were ruled out. Other anticoagulants and circulation-improving drugs were not administered.

Portal vein recanalization (i.e., complete resolution of the PVT and patency of portal vein blood flow) was indicated in patients with a decreased size of more than 50% of the portal vein thrombus and partial blood flow in the portal vein. Failure of portal vein recanalization was defined as no change in portal vein thrombus size and lack of blood flow in the portal vein.

Fondaparinux administration was discontinued following portal vein recanalization. Next, patients were prescribed medications for alternate antiplatelet aggregation (aspirin enteric-coated tablets; 100 mg, *q* 24 h).

2.4. Statistical analysis

Descriptive statistics included the interquartile range (IQR). Data were analyzed using the Wilcoxon signed-rank test. A P-value $< .05$ was considered statistically significant. The SPSS 17.0 software package was used for data analysis.

3. Results

3.1. The demographic details and disease characteristics

Patient 1: A 55-year-old woman diagnosed with decompensated cirrhosis associated to HBV presented with coagulation disorders and ascites. The patient had splenectomy 20 days ago due to hypersplenism. After the splenectomy, she gradually had abdominal distension and pain; *Patient 2*: A 48-year-old man diagnosed with decompensated cirrhosis associated to HBV presented with ascites, hepatorenal syndrome, jaundice, thrombocytopenia, and spontaneous bacterial peritonitis. The patient survived from variceal bleeding, and received splenectomy 1 month ago. He had abnormal liver function, coagulation disorders, and thrombocytopenia. The patient received combined therapy, including repeated large-volume paracentesis, terlipressin, albumins, diuretics, and antibiotics. However, he continued to have massive ascites; *Patient 3*: A 52-year-old woman diagnosed with decompensated cirrhosis associated to HBV presented with ascites, abnormal liver function, coagulation disorders, thrombocytopenia, and hypoproteinemia. The patient had variceal bleeding 15 days ago, and received endoscopic treatment; *Patient 4*: A 52-year-old alcohol-related cirrhotic man presented with spontaneous bacterial peritonitis, ascites, jaundice, coagulation disorders, and hypoproteinemia. He had partial splenic embolization 1 year ago. After the operation, he had been in the asymptomatic stage for more than 8 months. Two months ago, he gradually felt asthenia and abdominal distension; *Patient 5*: A 65-year-old woman diagnosed with decompensated cirrhosis associated to HBV presented with ascites. She had refractory ascites and oliguria; *Patient 6*: A 38-year-old HCV-related cirrhotic man had splenectomy after the hematemesis was controlled 17 days ago. Furthermore, he had fever and abdominal pain soon after the operation, and the antibiotic therapy was invalid; *Patient 7*: A 42-year-old woman diagnosed with decompensated cirrhosis caused by Budd–Chiari syndrome presented with hepatic encephalopathy. She underwent transjugular intrahepatic portosystemic shunt (TIPS) 3 month ago. After the procedure, she underwent regular screening by color Doppler ultrasound; and PVT occasionally found (Table 1).

3.2. Treatment outcomes

PVT disappeared completely and the target blood vessel was patent in 2 patients 7 days after drug administration, in 4 patients 14 days after drug administration, and in 1 patient 21 days after drug administration. The recanalization rate was 100%. Compared with data before treatment (Table 2), INR, PLT, and PT were not significantly reduced in any of the 7 patients. Furthermore, DD significantly declined during treatment (Table 3). In all 7 patients, PVT did not recur within one month after portal vein recanalization (Table 4). The portal vein was recanalized in all patients after treatment ($P = .018$). The decline in DD had a predictive value for portal vein recanalization ($P = .018$). No side effects such as bleeding, hypohepatia, or thrombocytopenia occurred in any of the patients ($P > .05$). Table 5 illustrates the statistical results. Bruising at the injection site occurred in one patient, but no additional minor or major adverse reactions occurred in the remaining patients.

Table 1

Patient demographics and disease characteristics.

Patient	Age	Gender	Child–Pugh	History of variceal bleeding	History of epigastric operation	Symptoms					
						Weight, kg	HE	Ascites	Jaundice	SBP	HS
1	55	W	B	N	Y	57	Y	Y	N	N	N
2	48	M	C	Y	Y	62	N	Y	Y	Y	Y
3	52	W	B	Y	N	71	N	Y	N	N	N
4	52	M	C	N	Y	62	N	Y	Y	Y	N
5	65	W	B	N	N	53	N	Y	N	N	Y
6	38	M	B	Y	Y	72	N	Y	Y	N	N
7	42	W	B	N	Y	68	Y	N	N	N	N

HE = hepatic encephalopathy, HS = hepatorenal syndrome, M = man, N = no, SBP = spontaneous bacterial peritonitis, W = woman, Y = yes.

Table 2

The data collected before the treatment.

N	PLT, 10^9/L	PT, S	DD	INR, μg/mL	ALT, U/L	AST, U/L	ALB, g/L	TBIL, μmol/L	Width of PV, mm	Size of thrombosis, mm × mm
1	396	13.10	12.610	1.16	35	46	34.2	15.8	13	21 × 6
2	25	19.50	8.650	1.71	30	45	23.5	29.8	14	22 × 9.7
3	24	12.10	5.710	0.88	72	98	29.1	12.7	12	79 × 7.4
4	237	9.60	2.074	2.38	69	99	24.2	147.0	13	45 × 13
5	61	27.40	6.600	1.07	11	31	36.0	49.0	10	27 × 6
6	133	16.50	11.250	1.37	26	65	33.5	24.6	15	65 × 4.3
7	310	11.20	0.420	1.00	39	37	36.3	9.0	13	16 × 13

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DD = D dimer, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, PV = portal vein, TBIL = total bilirubin.

Table 3

The data collected when the portal vein recanalization.

N	PLT, 10^9/L	PT, S	DD	INR, μg/mL	ALT, U/L	AST, U/L	ALB, g/L	TBIL, μmol/L	Width of PV, mm	Velocity, cm/s	Days, d
1	299	12.10	3.797	1.06	35	47	34.1	14.3	13	14	21
2	21	19.20	0.930	1.68	33	25	26.8	37.4	14	19	14
3	61	12.20	1.340	1.08	35	50	34.4	24.4	12	14	14
4	211	10.20	0.388	0.93	39	91	28.6	67.7	12	10	7
5	76	23.60	0.769	2.36	18	90	39.0	178.0	12	12	7
6	153	16.20	3.199	1.35	16	40	33.1	40.8	11	15	14
7	268	10.10	0.215	0.92	26	24	38.4	8.9	12	19	14

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DD = D dimer, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, PV = portal vein, TBIL = total bilirubin.

4. Discussion

PVT can easily be overlooked, and misdiagnosis can occur due to its low incidence, atypical symptoms and lack of physical signs during the early stages. The majority of patients seek medical help, because portal vein obstruction causes portal hypertension; leading to intestinal congestion, abdominal pain, and/or gastrointestinal bleeding. As the popularity of color Doppler ultrasound and CT scanning increased in recent years, the detection rate of PVT has improved. In patients with cirrhosis,

Table 4

The data collected 1 month after portal vein recanalization.

N	PLT, (10^9/L)	PT, S	DD	INR, μg/mL	ALT, U/L	AST, U/L	ALB, g/L	TBIL, μmol/L	Width of PV, mm	Velocity, cm/s
1	299	11.20	1.261	1.00	66	67	34.5	9.3	13	14
2	43	17.00	0.930	1.41	30	39	26.9	47.7	14	17
3	82	16.50	1.370	1.10	62	85	29.2	18.2	12	14
4	329	9.00	0.474	0.84	48	68	29.9	47.1	12	12
5	84	16.70	0.930	1.39	27	50	36.6	198.0	12	12
6	158	17.00	0.918	1.41	21	31	36.0	31.3	12	15
7	258	9.30	0.350	1.24	15	20	34.1	6.6	11	25

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DD = D dimer, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, PV = portal vein, TBIL = total bilirubin.

Table 5

The statistical result.

Group	PLT	PT	DD	INR	ALT	AST	ALB	TBIL	Width of PV	Velocity
Before	285	8.3	9.180	0.71	43	61	11.2	134.3	1	0
After	207	9.0	2.811	0.75	17	64	9.8	54.4	1	7
P-value	.612	.236	.018	.236	.116	.310	.063	.499	1.000	.018

Descriptive statistics included the interquartile range (IQR). The data were analyzed using the Wilcoxon signed-rank test. A *P*-value $< .05$ indicated a statistically significant difference.
ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, DD = D dimer, INR = international normalized ratio, PLT = platelet, PT = prothrombin time, PV = portal vein, TBIL = total bilirubin.

disease progression following PVT is rapid; and leads to refractory recurrent upper gastrointestinal bleeding and ascites in some patients. This progressive disease can lead to intestinal necrosis, and its fatality rate can reach up to 50%.[8] Both embolectomy and liver transplantation are effective surgical choices for the treatment of PVT. However, patients with decompensated cirrhosis cannot undergo surgical treatment due to either severe liver dysfunction or lack of matching liver donors. During the early stages of thrombosis, thrombolytic therapy can achieve good outcomes; but increased dosing may be required and the probability of intestinal bleeding may increase.[9–11] Furthermore, indications for thrombolytic therapy should be strictly acknowledged.[12] Patients with decompensated cirrhosis may not meet the indications for thrombolytic therapy due to grade C liver function according to Child–Pugh classification, history of gastrointestinal bleeding, thrombocytopenia, and coagulation disorders.

Studies have shown that spontaneous recanalization of PVT is rare, and anticoagulants should be used as long as there are no contraindications for anticoagulation therapy.[13] Anticoagulation has good results for the treatment of PVT. In patients with acute PVT, the recanalization rate of the portal vein is >80% following anticoagulation therapy.[14,15] Commonly used anticoagulants are warfarin and low-molecular-weight heparin. The oral administration of warfarin can be easily accepted by patients, but INR needs to be monitored to adjust to the appropriate dose. It has generally been believed that the effective INR range for anticoagulation is 2-3, but the INR of patients with cirrhosis is usually ≥2. Therefore, dose adjustment based on INR values may not be suitable for anticoagulation. The half-life of warfarin is long, and long-term applications can cause bleeding.[16–18] INR is one of the indicators in the model of end-stage liver disease (MELD) scale. Currently, the MELD scale is applied to determine the order in which patients are offered liver transplantation in the United States, and the "man-made" changes to INR caused by anticoagulant therapy can negatively affect that pecking order. Heparin and low-molecular-weight heparin can bind to serum proteins, macrophages and endothelial cells; and the inhibition of those anticoagulants on thrombin is incomplete and unstable. Individual patient response is highly variable, and side effects such as heparin-induced thrombocytopenia (HIT) and bleeding can and do occur.[19] The anticoagulation effects of heparin are poor in some patients. Studies have shown that more than 20% of all DVTs progress and ultimately affect nearby blood vessels, even after the administration of low-molecular-weight heparin anticoagulation. Furthermore, the thrombus becomes persistent after 1 year of continuous anticoagulation therapy. In patients with decompensated cirrhosis, hypersplenism can induce thrombocytopenia, and impaired liver synthesis capacity causes coagulation disorders. Thus, there are some risks associated with the application of conventional anticoagulants. Other anticoagulants such as thrombin inhibitors and factor Xa inhibitors remain in the development stage, but are promising options in the future.[20]

Fondaparinux is a relatively new highly selective factor Xa inhibitor. It exerts its function primarily through the specific inhibition of antithrombin on Xa. Fondaparinux is available as an injectable formulation, with a half-life of 17 to 21 hours (requiring once daily administration). Its syringe has a unique spring-latch structure, and the needle can rebound quickly after injection, thereby reducing the concentration of the drug in the superficial subcutaneous tissue, reducing irritation to the local tissue, and reducing the incidence of bleeding. Fondaparinux binds to antithrombin, and specifically and selectively acts on Xa. Unlike unfractionated heparin and low-molecular-weight heparin, fondaparinux does not bind to platelet factor IV or form HIT antibodies. Therefore, the risk of HIT is rare in clinical practice. Studies on the safety and efficacy of fondaparinux in the prevention of lower-limb DVT and pulmonary embolism has confirmed that its efficacy is the same as, or superior to, that of low-molecular-weight heparin. Two clinical trials (the OASIS-5 and -6) confirmed that the anticoagulation efficacy of fondaparinux is comparable to both heparin and low-molecular-weight heparin in unstable angina, and it is notable in those studies that the incidence of severe bleeding was significantly reduced.[21] During the literature review of the authors, no reports regarding the application of fondaparinux in PVT were identified. Based on the mechanism of thrombosis formation and the functional mechanism of fondaparinux, the authors speculate that fondaparinux should have a good therapeutic value for PVT.

In this study, portal vein recanalization was achieved in all 7 cases within 21 days of fondaparinux anticoagulation treatment. Compared with the study of Amitrano et al,[22] the time to recanalization in this study was significantly shorter. Due to the lack of clinical data on the long-term use of fondaparinux sodium and information regarding the use of this drug in patients with poor liver function, fondaparinux was subsequently changed to aspirin, which focuses on the mechanism of thrombus formation. No recurrence of PVT occurred in any patient during the 1 month of follow-up period.

This study revealed that INR, PLT, and PT were not significantly different before and after treatment, confirming that fondaparinux did not significantly affect INR, PLT, and PT during the treatment of PVT. Furthermore, fondaparinux did not significantly increase the risk of bleeding. DD is an antigenic determinant in fibrin, which is present in fibrin degradation products (but not in the degradation products of fibrinogen). It is a specific molecular marker for fibrin formation and degradation in the body. A sustained elevated DD concentration may indicate an active coagulation and fibrinolysis processes in the body. In this study, DD was significantly different before and after treatment, indicating that dynamic DD detection during the formation of PVT is a predictive value for the diagnosis of PVT and therapeutic results. In clinical cases, when DD is significantly

elevated, imaging of the portal vein and anticoagulant therapy are indicated.

Coagulation disorders/thrombocytopenia is present in patients with decompensated cirrhosis, and liver function in these patients is typically poor. In clinical practice, surgery, drug-induced and interventional thrombolysis, and heparin or low-molecular-weight heparin anticoagulant therapy may not be suitable for such patients. In this study, 7 patients were treated with fondaparinux anticoagulation therapy, and portal vein recanalization rate was 100%.[6,22] Together, those results confirm that fondaparinux is safe and effective for the treatment of acute PVT in patients with decompensated cirrhosis.

4.1. Shortcomings and prospects of this study

As it is known, Doppler ultrasound is not ideal for defining the extent of the PVT, and in defining complete recanalization. It is a pity that in this study, we used Doppler ultrasound for financial reasons. We should use MRI to observe PVT in the following studies. It is notable that the number of cases and the duration of follow-ups were limited in this study. Furthermore, the sample size should be increased in future studies to explore the efficacy of fondaparinux for the treatment of acute PVT in patients with decompensated cirrhosis. Its long-term efficacy and adverse reactions also requires further studies.

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