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Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis

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ABSTRACT

Background and aim: Anticoagulation therapy is the main line of treatment for acute portal vein thrombosis (PVT) in the absence of cirrhosis. However, the use of this therapy in cirrhotic PVT is still with doubtful evidence. We aimed to evaluate the efficacy and safety of rivaroxaban compared to warfarin for the management of acute non-neoplastic PVT in Hepatitis C virus (HCV)–related compensated cirrhosis.

Methods: Out of 578 patients with chronic HCV infection, 80 patients with acute PVT who had undergone splenectomy due to hypersplenism and 4 patients with acute PVT due to portal pyemia were selected. The patients were randomly assigned (1:1) to the study group (n = 40), in which the patients received rivaroxaban 10 mg/12 h, or the control group (n = 40), in which the patients received warfarin.

Results: In the rivaroxaban group, the resolution of PVT was achieved in 34 patients (85%) within 2.6 ± 0.4 months and delayed, partial recanalization after 6.7 ± 1.2 months (n = 6.15%). Complications such as major bleeding, abnormal liver functions, death, or recurrence did not occur during treatment, and patients in this group showed improved short-term survival rate (20.4 ± 2.2 months) compared to the survival rate in the control group (10.6 ± 1.8 months) in which warfarin achieved complete resolution in 45% of patients. Complications such as severe upper GI tract bleeding (43.3%), hepatic decompensation (22.5%), progression to mesenteric ischemia (12.5%), recurrence (10%), and death (20%) were observed in the control group. The duration until complete resolution of thrombus correlated with age, the extent of the thrombus, creatinine level, and MELD score. The recurrence after complete resolution of thrombus correlated with age, the extent of the thrombus, thrombogenic gene polymorphism, and the use of warfarin.

Conclusion: Rivaroxaban was effective and safe in acute HCV-related non-neoplastic PVT with improved short-term survival rate; ClinicalTrials.gov Identifier: NCT03201367.

1. Introduction

Portal vein thrombosis (PVT) could be due to neoplastic growth invading the portal vein (PV) or non-neoplastic causes. The predisposing factors include sluggish portal blood flow [1] and portal pyemia secondary to appendicitis, diverticulitis, inflammatory bowel disease, pancreatitis, and cholangitis. Occasionally, PVT might be instigated by surgical trauma after portosystemic shunt operations, liver transplantation, and loco-regional therapy for hepatocellular carcinoma (HCC) [2]; splenectomy and endoscopic variceal sclerotherapy may be complicated by PVT [3].

PVT might be associated with hereditary hypercoagulable states such as factor V Leiden mutation, prothrombin gene 20,210 mutations, myeloproliferative disorders, and antiphospholipid syndrome [4]; however, idiopathic PVT might be encountered in approximately 25% of patients with PVT [5].

Patients with acute PVT usually have no sufficient time for the development of adequate collaterals. Ascites, which develops after acute PVT, is mild and transient because of intestinal congestion and is associated with decreased long-term survival rate [6,7].

The aim of treatment is to achieve complete recanalization of the PV before the event of irreversible parenchymatous and mesenchymal complications. The rate of recanalization may approach 70% if treatment is initiated within one week of the onset of acute PVT; however, it may fall to 25–30% if initiated later [8].

Treatment of PVT depends mainly on its acuity, expansion to the

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superior mesenteric vein (SMV) with progressive ischemia, if there is a documented hereditary thrombophilia, in candidates for liver transplantation with a high risk PVT that shows obstruction of > 50% of the PV [9, 10].

Rivaroxaban is an orally active direct inhibitor of factor Xa; it is adequately absorbed from the gut, with the maximum inhibition of factor Xa after 4 h since ingestion [11].

The aim of the current study is to evaluate the efficacy and safety of rivaroxaban compared to warfarin for the management of acute non-neoplastic PVT in patients with Hepatitis C virus (HCV)-related compensated cirrhosis and the impact of treatment on the prevention of complications, PVT recurrence, and survival.

2. Methods

This randomized, controlled, interventional, open-label study was conducted in the Hepatology Clinic – Internal Medicine and Tropical Medicine Departments, Zagazig and Tanta University Hospitals, which are tertiary referral centers, from May 2014 to August 2017.

Eighty patients with chronic HCV and PVT were enrolled after fulfilling the inclusion criteria. Out of 578 patients, 4 patients with chronic HCV and PVT due to portal pyemia secondary to infected thrombosed internal piles (n = 1), appendicular abscess (n = 1), ulcerative colitis (n = 2), which was diagnosed by abdominal ultrasonography (USG), were included. In addition, 76 patients (13.1%) with chronic HCV who had undergone splenectomy through an open surgery due to marked splenomegaly that caused intolerable abdominal pain and severe thrombocytopenia ($34.6 \pm 12.8 \times 10^3$/μl) were selected.

Diagnosis of acute PVT was confirmed during the postoperative period; the risk factors for postoperative PVT were severe preoperative thrombocytopenia, large size of the spleen (21.8 ± 2.1 cm), large splenic vein diameter (10.3 ± 1.7 mm) with numerous splenic collaterals, rebound postoperative increase in the platelet count ($562.5 \pm 37 \times 10^3$/μl) that occurred in 32 patients (42.1%), and lack of perioperative prophylactic anticoagulation. Patients provided past history of receiving treatment for HCV and achieved sustained virological response. The treatment included direct-acting antiviral-based therapy for 3 months (n = 37) or pegylated interferon and ribavirin for 48 weeks (n = 43).

The 80 included patients were randomly assigned (1:1) to either a study group who received rivaroxaban (n = 40) or a control group who received warfarin (n = 40). Both groups were given symptomatic therapy for ascites and abdominal pain, and the patients were followed up synchronously to evaluate the impact of therapy on the occurrence of complications and survival rate. Approval was obtained from the Ethical Committee, Faculty of Medicine, Zagazig University, in February 2014 before the start of the study; the study was registered on clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03201367).

Patients with acute non-neoplastic PVT (acute PVT that was diagnosed within 1 week of onset), chronic HCV, and compensated liver disease (Child class A-B) were included in the study.

Patients with advanced liver disease or alanine transaminase (ALT) levels more than three times the upper limit of the normal (ascites due to vascular occlusion is not an exclusion criterion), recent bleeding due to active peptic ulcer or esophageal varices (EV), neoplastic invasion of the PV, creatinine clearance ≤30 ml/min, pregnancy and breast-feeding, hypersensitivity to rivaroxaban, concomitant treatment with other anticoagulants, concomitant use of clopidogrel, and reduced life expectancy were excluded from the study.

All patients enrolled in the study were subjected to routine investigations preliminary to splenectomy, such as liver function tests, coagulation profile, renal function tests, complete blood count, reticulocyte count, and bone marrow aspiration. For each patient, Child-Pugh (CTP) and MELD scores were calculated. Patients were tested for thrombogenic gene polymorphisms such as factor V Leiden mutation and prothrombin gene 20,210 mutations.

Abdominal USG was done for all patients included in the study. Cirrhotic echo pattern and criteria of portal hypertension were determined from the coarse nodular appearance, prominent caudate lobe, splenomegaly with a splenic bipolar diameter > 130 mm, and splenic vein diameter > 10 mm. Patients with HCC were excluded due to reduced life expectancy.

Color Doppler USG was performed by one experienced radiologist with the use of real-time portable ultrasound equipment (Sonoscape S9) consisting of a color Doppler and a pulsed Doppler device working at 3.5-MHz frequency to confirm the diagnosis of PVT.

CT angiography was done for all patients for leveling of PVT to determine the duration of thrombolytic therapy and clinical outcome. PVT was classified into thrombosis confined beyond the confluence of the splenic vein and SMV; to the SMV, but with patent other mesenteric vessels; to the whole splanchnic venous system, but with large collaterals; or extensive splanchnic venous thrombosis with only minute collaterals [12].

Before splenectomy, upper GI tract endoscopy was done to document the presence and grading of EV. EVs with signs of risk were managed with endoscopic band ligation (EBL), and splenectomy was postponed until at least two sessions of band ligation were performed within 2 months of duration.

2.1. Protocol of therapy

CT angiography was done for leveling of PVT and to determine the duration of thrombolytic therapy. Both groups were managed with enoxaparin at a dose of 1 mg/kg every 12 h subcutaneously for 3 days; then, the study group was treated with rivaroxaban 10 mg/12 h [13] to avoid possible liver injury with the full dose of rivaroxaban [14], as the selected patients had chronic HCV with an underlying chronic liver disease. Rivaroxaban was started 2 h before the next dose of enoxaparin.

Patients in the control group were primed with enoxaparin 1 mg/kg every 12 h subcutaneously for 3 days and then maintained on warfarin to maintain international normalized ratio (INR) at a level of 2–2.5.

- Follow-up was done every week with questionnaires about symptoms of bleeding (hematemesis, melena, epistaxis, gum bleeding, vaginal bleeding, and subcutaneous bleeding) and worsening or improvement of abdominal pain. Patients were instructed to inform the study center immediately if any of these symptoms had occurred.
- Bedside USG was done to detect thrombus resolution every 2 weeks until recanalization of PVT and then every 2 months for 1 year to detect PVT recurrence.
- Laboratory follow-up was done every 2 weeks during treatment, which included serum creatinine level, complete blood count, and liver function tests to detect whether there are any side effects of the therapy.

2.2. Outcome definition

The primary efficacy outcome is the complete recanalization of the PV or partial recanalization if reopening is > 50% of the luminal occlusion, and the secondary efficacy outcome is the absence of recurrence after termination of therapy.

The primary safety outcome is major bleeding defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartmental syndrome and/or bleeding that causes a decrease in the hemoglobin level by 2 g/dl or more or leads to the transfusion of two or more units of whole blood or red cells [15, 16]. Abnormalities in the liver functions and death due to bowel infarction, bleeding, or acute liver cell failure were recorded.

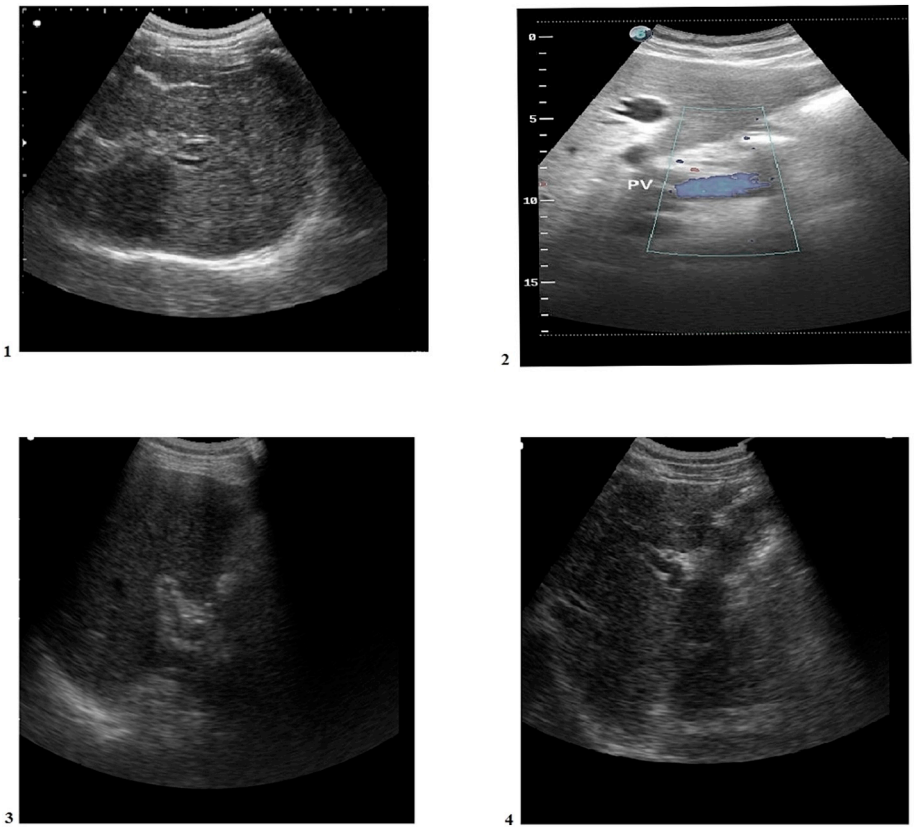

Fig. 1. 1: Abdominal ultrasonography reveals cirrhotic liver with complete portal vein thrombosis. 2: Color Doppler ultrasonography reveals portal vein thrombosis. 3: Abdominal ultrasonography reveals complete portal vein recanalization after treatment with rivaroxaban. 4: Abdominal ultrasonography reveals complete portal vein recanalization after treatment with rivaroxaban.

2.3. Statistical analysis

Data were statistically analyzed using SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± SD. Categorical variables were analyzed using the χ^2 test, and continuous variables were analyzed using the Student's *t*-test. Correlation analysis was expressed as Pearson's correlation coefficient (r). $P < 0.05$ was considered statistically significant. Kaplan–Meier survival curves were generated to detect the impact of rivaroxaban and warfarin on patients' survival rate and the occurrence of life-threatening complications.

3. Results

Eighty patients who had chronic HCV and presented with acute PVT (67 males and 13 females) (Fig. 1 1, 2) with a mean age of 43.2 ± 3.8 years were included. Their baseline characteristics are shown in Table 1.

Preoperative screening for EVs was done, and EVs were managed by EBL. No one received preoperative administration of prophylactic anticoagulants to avoid the risk of bleeding from EV or congestive gastropathy.

In the study group, rivaroxaban was effective with rapid resolution of acute PVT within 2.6 ± 0.4 (2–3.8) months in 34 patients (85%). Six patients showed delayed and partial resolution (> 50% of the lumen) after 6.7 ± 1.2 months, with highly significant improvement in abdominal pain, fever, vomiting, and disappearance of ascites (Table 2, Fig. 1 3, 4). To avoid recurrence, we extended the anticoagulant therapy for one month after complete recanalization when PVT was limited beyond the confluence of the splenic vein and SMV (n = 24) and for 2 months if it involved SMV (n = 12) or the whole splanchnic venous system (n = 4) and for 6 months in patients with a positive thrombogenic gene assay result (n = 2, 5%) or with partial recanalization (n = 6).

No one experienced major bleeding during treatment with no recorded elevation of serum transaminases or total bilirubin. Significant improvements were observed in transaminase levels, CTP score, and MELD score, with a highly significant improvement in D-dimer (Table 2). Follow-up extended to 1 year through USG every 2 months and repeated clinical assessment; no one experienced recurrence of PVT, hepatic decompensation, or recorded mortality.

Table 1
Baseline demographic, symptomatic, laboratory and endoscopic characteristics of the study and control populations after splenectomy and before anticoagulation.

Variable	Study group before therapy	Control group before therapy	P
Age (years)	46 ± 5	41.3 ± 2.3	0.2
M/F	32/8	35/5	0.12
Abdominal pain (n=)	40 (100%)	40 (100%)	–
Fever (n=)	40 (100%)	40 (100%)	–
Vomiting (n=)	16 (40%)	22 (55%)	0.04
Ascites (n=)	6 (15%)	4 (10%)	0.1
Platelets (10^3/μl)	462.5 ± 37	480 ± 75	0.063
INR	1.2 ± 0.04	1.1 ± 0.2	0.5
PC %	72 ± 3	69 ± 2.3	0.19
Albumin (gm/dl)	3.4 ± 0.3	3.5 ± 0.4	0.12
Total bilirubin (mg/dl)	1.5 ± 0.14	1.4 ± 0.4	0.64
AST (IU/l)	73.8 ± 19.1	46 ± 12	0.043
ALT (IU/l)	77.7 ± 13.1	72 ± 10.6	0.3
Creatinine (mg/dl)	1.1 ± 0.34	1 ± 0.4	0.26
D.dimer (ng/ml)	853 ± 87.4	634 ± 41	0.01
CTP	6.4 ± 0.4	6.2 ± 0.3	0.4
MELD	10.5 ± 1.4	9.75 ± 1.1	0.1
Endoscopy (n = 76)			
EV1 (20)	(n = 11, 27.5%)	(n = 9, 23.3%)	0.2
EV2 (22)	(n = 4, 10%)	(n = 18, 45%)	0.001
EV3-4 (34)	(n = 23, 57.5%)	(n = 11, 27.5%)	0.001

CTP: Child Turcot Pugh, MELD: Model for end stage liver disease.

Table 2
Outcome after therapeutic anticoagulation in the study and control populations.

Variable	Study group after therapy	Control group after therapy[a]	P
Complete recanalization (n=, onset)	34 (85%, 2.6 ± 0.4 months)	18 (45%,4.3 ± 1.4 months)	0.001
Partial recanalization (n=, onset)	6 (15%, 6.7 ± 1.2 months)	0	0.001
Ascites (n=)	0 (0%)	9 (41%)	0.001
GIT bleeding	0 (0%)	17 (43.3%)	0.001
Hepatic encephalopathy	0 (0%)	7 (31.8%)	0.003
Intestinal infarction	0 (0%)	2 (9.1%)	0.003
Death	0 (0%)	8 (36.4%)	0.001
Platelets (103/μl)	320 ± 45	213 ± 15	0.02
INR	1.1 ± 0.2	2.4 ± 0.5	0.02
PC %	67 ± 2.3	54 ± 0.9	0.036
Albumin (gm/dl)	3.8 ± 0.4	2.9 ± 0.2	0.02
Total bilirubin (mg/dl)	1.2 ± 0.4	2.4 ± 0.3	0.04
AST (IU/l)	46 ± 12	67 ± 18	0.023
ALT (IU/l)	52 ± 9	60 ± 4	0.03
Creatinine (mg/dl)	0.9 ± 0.4	1.9 ± 0.8	0.02
D.dimer (ng/ml)	234 ± 24.6	456 ± 100	0.004
CTP	6 ± 0.4	9.7 ± 0.8	0.002
MELD	7.5 ± 0.9	24 ± 1.2	0.000

CTP: Child Turcot Pugh, MELD: Model for end stage liver disease.
[a] Laboratory values are of the complicated cases in the control group (n = 22).

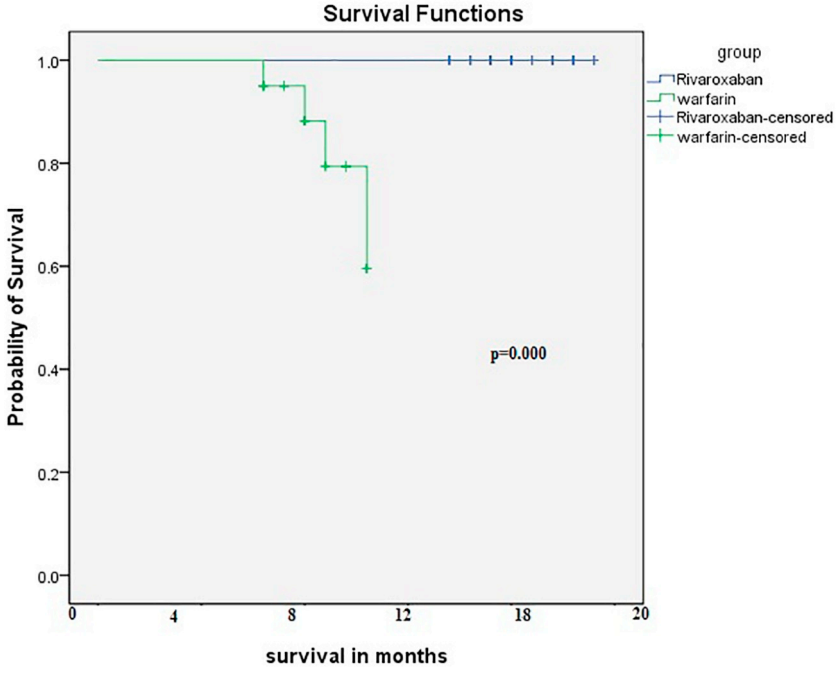

Fig. 2. A Kaplan–Meier plot for evaluating the survival rate in the study and control groups.

In the control group, all patients had received warfarin at a dose of 3.1 ± 1.2 mg daily and INR was optimized at 2.2 ± 0.45. During the follow-up, 17 patients (43.3%) developed severe attacks of upper GI tract bleeding (UGIB); hence, warfarin administration was stopped, and endoscopy was performed to reveal bleeding EV managed with EBL (n = 14) or amacrylate injection for bleeding fundal varix (n = 3). Progression of mesenteric ischemia had occurred in five patients (12.5%) who were shifted to rivaroxaban according to the protocol. Eighteen patients (45%) achieved complete resolution of the thrombus after 4.3 ± 1.4 months, Maintenance therapy was extended for one month after recanalization if PVT was limited beyond the confluence of the splenic vein and SMV (n = 34), for 2 months if PVT involved the SMV (n = 5), the whole splanchnic venous system (n = 1), or for 6 months with a positive thrombogenic gene assay result (n = 1, 2.5%).

In the control group, complications occurred (n = 22, 55%); nine (41%) patients developed moderate ascites, which was resistant to diuresis. Jaundice and hepatic encephalopathy (HE) was observed in seven (31.8%) patients (HE grade II in two patients and grade III in five patients). Death occurred in eight (36.4%) patients after 2.3 ± 0.8 months owing to uncontrolled UGIB (n = 6) and intestinal infarction (n = 2). Recurrence occurred in 4/18 (22.2%) patients who had a positive thrombogenic gene assay result (n = 1), ulcerative colitis (n = 1), and PVT involved the SMV (n = 2) (Table 2).

The duration until complete resolution of thrombus correlated with age (r = −0.481, p = 0.001), the extent of the thrombus (r = 0.435, p = 0.003), creatinine level (r = −0.658, p = 0.000), and MELD score (r = −0.651, p = 0.000), thus denoting that older age, higher creatinine level, higher MELD scores, and more extensive thrombus were associated with a lower chance and longer duration until complete recanalization of PVT.

The recurrence after complete resolution of thrombus correlated with age (r = 0.345, p = 0.007), the extent of the thrombus (r = 0.635,

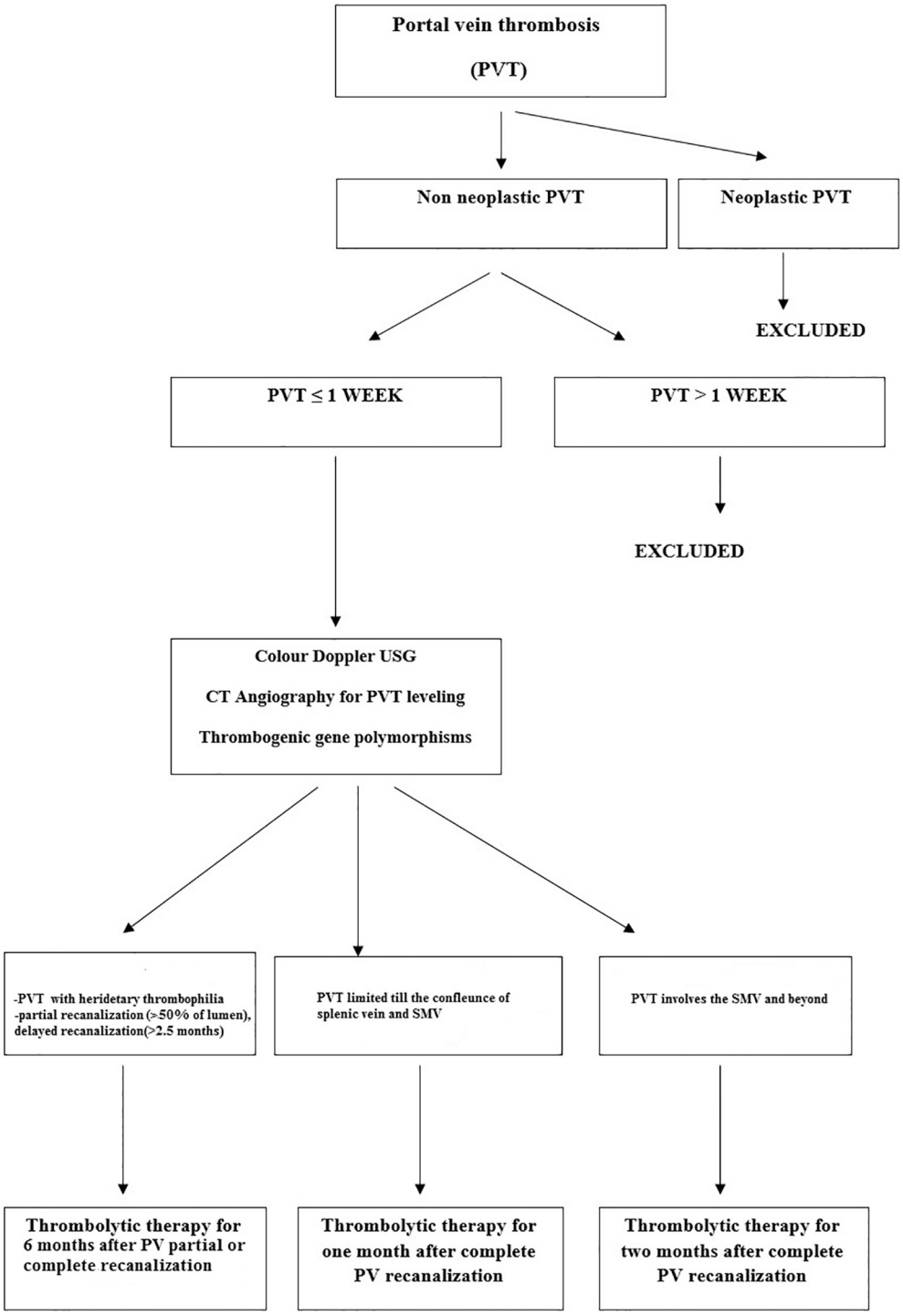

Fig. 3. A postulated treatment algorithm for acute non-neoplastic portal vein thrombosis.

p = 0.000), thrombogenic gene polymorphism (r = 0.568, p = 0.001), and the use of warfarin (r = 0.459, p = 0.003).

The last case was enrolled at April 2016. The Kaplan–Meier survival curve was generated to evaluate the survival rate, and curve details revealed that patients who were treated early with rivaroxaban had a better survival rate, which was calculated from the onset of diagnosis of PVT without major complications or death (20.4 ± 2.2 months) vs. (10.6 ± 1.8 months) in the warfarin group (p = 0.001) (Fig. 2). A postulated treatment algorithm was constructed as shown in Fig. 3.

4. Discussion

The use of anticoagulation in cirrhotic PVT is still with doubtful evidence. Approximately 83% of acute PVT does not recanalize spontaneously unless an anticoagulant was introduced [17]. The postulated advantage of direct oral anticoagulants in chronic liver disease is that their activity is independent of antithrombin III, which is reduced in liver cirrhosis [17].

The previous trials showed a partial response to anticoagulation and a longer duration until the appearance of the therapeutic effects, thus exposing the patients to the side effects of anticoagulation [18,19].

Vitamin K antagonists have a rate of complete PV recanalization in 40–45% of patients after a mean duration of 6 months [20]. Heparin may be suboptimal owing to the impaired production of antithrombin III in liver cirrhosis. Low-molecular-weight heparin (LMWH) similar to enoxaparin resulted in complete PV recanalization in 33% of patients after 6 months of treatment and in 75% of patients with extension of the duration to another 6 months [19], however, with difficult dose estimation in the presence of ascites and edematous tissues [20].

Thrombolytic therapy delivered by invasive methods such as through the systemic venous circulation, the superior mesenteric artery, or the PV through trans-jugular or trans-hepatic approach were attempted; however, the efficacy was lower and mortality rate was higher when compared to those by the conservative treatment [20, 21, 22].

The current study evaluated the effect of low-dose rivaroxaban on acute PVT in patients with underlying chronic liver disease due to HCV, thus aiming to get higher rates of recanalization in shorter periods to avoid or minimize the possible risk of hepatotoxicity and side effects of medications.

The efficacy of rivaroxaban was compared to that of warfarin regarding the time until complete recanalization and prevention of life-threatening complications after acute PVT; and the results revealed that rivaroxaban was tolerated with rapid resolution of PVT within 2.6 ± 0.4 months in 85% of patients; however, 15% of patients showed delayed and partial recanalization after 6.7 ± 1.2 months with the advantage of significant improvement in abdominal pain; fever; and prevention of parenchymatous decompensation, mainly ascites and HE, or vascular decompensation such as portal hypertension and variceal bleeding.

Warfarin was associated with recanalization in 45% of patients after 4.3 ± 1.4 months, with a significant increase in complications such as severe UGIB (43.3%), mesenteric ischemia (12.5%), liver cell failure (22.5%), and death (20%) due to UGIB and intestinal infarction. Recurrence was significantly higher with warfarin along with a significantly lower survival rate (10.6 ± 1.8 vs. 20.4 ± 2.2 months in the rivaroxaban group, $p = 0.000$).

Successful treatments of PVT with rivaroxaban without recorded side effects and with rapid clot lysis were previously reported [23,24,25].

A larger study was conducted on 39 patients with cirrhosis who received anticoagulation therapy in the form of direct oral anticoagulants ($n = 20$) or traditional anticoagulation therapy ($n = 19$), and this study confirmed that the first group had a safety profile similar to that of traditional anticoagulation therapy [26]. Potze et al. concluded that rivaroxaban and apixaban in liver cirrhosis would not result in an increased risk of bleeding [27]. A multicenter study concluded that direct oral anticoagulants had fewer side effects with no alteration in renal and liver functions during treatment [28].

The current study included an adequate number of patients from two centers, with a sufficient period of follow-up when compared to the previous studies.

In conclusion, rivaroxaban was effective and safe in HCV-related acute non-neoplastic PVT, with improved short-term survival rate, and we recommend propagating its use in this category of patients.

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Declaration of personal interests

The authors declare that they have no conflict of interest.

Guarantor of the article

Amr Shaaban Hanafy.

Author contributions

Amr Hanafy designed the research and statistical analysis. Amr Hanafy and Sherief Abd-Elsalam collected clinical data from the patients. Amr Hanafy drafted the manuscript. Mohammed Dawoud supervised the radiological investigations. Revisions to the manuscript were made by all authors.

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