

Exploring the Outcomes of Portal Vein Thrombosis in the Clinical Setting of Cirrhosis, Malignancy, and Intra-abdominal Infections with and without Anticoagulation: A Retrospective 5-Year Study

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Abstract

The aim of this study was to understand the differences in clinical outcomes in portal vein thrombosis (PVT) patients with cirrhosis, malignancy, and abdominal infections, with or without anticoagulation. This study was approved by ethics committee. Data were collected from 2011 to 2016. Patients were classified into three groups: PVT with cirrhosis, malignancy, and infections. Primary outcomes measures collected were clot resolution, bleeding, recurrence, and death. Frequency, means, and percentages were calculated. In total, 30 patients were analyzed in this study. Mean age was 60.8 years (range of 30–91 years). There were 19 (63.3%) males and 11 (36.7%) females with ethnicity: 21 (70.0%) Chinese, 2 (6.7%) Malay, 2 (6.7%) Indian, and 5 (16.7%) other race. Fifteen patients received anticoagulation and 15 did not receive anticoagulation. Of the 15 patients who received anticoagulation, there was complete resolution of thrombus in 5 (33.3%), partial resolution in 1 (6.7%), and no resolution in 9 (60.0%). Of these 15 patients, there was bleeding in 3 (20.0%), there was no recurrence in 9 (60.0%), and 3 (20.0%) died during the period of follow-up. Of the 15 patients who did not receive anticoagulation, there was complete resolution of thrombus in 2 (13.3%), partial resolution in 0 (0.0%), and no resolution in 13 (86.7%). Of these 15 patients, there was bleeding in 0 (0%), there was recurrence in 2 (13.3%), and 6 (40.0%) died during the period of follow-up. Anticoagulation is effective in PVT. It reduces mortality with lower rate of recurrence. However, it is associated with increased risk of bleeding.

Keywords

- ▶ thrombophilia
- ▶ portal vein thrombosis
- ▶ anticoagulation
- ▶ low molecular weight heparin

Portal vein thrombosis (PVT) is a potentially life-threatening ailment stems from multiple factors, both local and systemic prothrombotic risk factors.¹ Patients may present asymptotically or within life-threatening intestinal infarction. Conditions including cirrhosis, malignancy, and abdominal infections may precipitate thrombus formation, and lead to complications of intestinal ischemia, portal cholangiopathy, portal hypertension, and death.²

The use of anticoagulants in PVT poses a risk to patients with any ailment because of increased risk of gastrointestinal bleeding with portal hypertension.³ Current guidelines are unclear on the efficacy of anticoagulant therapy in patients with PVT.^{4,5} Exploring the outcomes of all three groups of patients with and without the use of anticoagulants will highlight the possible effectiveness and safety of this treatment, helping guide treatment in the future.

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Aim

The aim of this study was to understand the differences in clinical outcomes in PVT patients with cirrhosis, malignancy, and abdominal infections, with or without anticoagulation.

Method

This study was approved by ethics committee (Domain Specific Review Board, Singapore). Data were collected from inpatient referrals to the Department of Vascular Medicine, General Medicine, Tan Tock Seng Hospital, for PVT, from 2011 to 2016.

Patients were classified into three groups:

1. PVT with cirrhosis
2. PVT patients with primary or secondary liver malignancy
3. PVT patients with intra-abdominal infections

Patients excluded were those with missing data for primary outcome measures or those with overlap of PVT for two or more conditions. Demographic data along with various comorbidities including diabetes, hypertension, previous thrombotic events, and hypercoagulable states were collected. Data were also collected for extent of PVT occlusion and additional vein occlusions. Primary outcomes measures collected were clot resolution, bleeding, recurrence, death in all three groups, and overall with or without anticoagulation.

Frequency, means, and percentages were calculated and the data across each subgroup were compared with the variables of use of anticoagulant therapy compared with those who did not receive.

Results

Data were analyzed for 36 patients. Four patients were lost to follow-up, two patients were excluded as they had both cirrhosis and intra-abdominal infections, and it was difficult to classify them. In total, 30 patients were analyzed in this study.

Mean age was 60.8 years (range of 30–91 years). There were 19 (63.3%) males and 11 (36.7%) females with ethnicity: 21 (70.0%) Chinese, 2 (6.7%) Malay, 2 (6.7%) Indian, and 5 (16.7%) other race. Patients developing PVT from malignancy in this group were 13 (43.4%), 13 (43.4%) with infections, and 4 (13.3%) with cirrhosis. Out of 30 patients overall, 15 received anticoagulation and 15 did not receive anticoagulation. The data on demographic, comorbidities, investigations, complications, and outcomes are summarized in ► **Table 1**.

Comparing the subgroups of those who received anticoagulation to those who did not receive anticoagulation, mean age was 55.6 years compared with 66 years. The group of 15 who received anticoagulation therapy had a higher proportion of intra-abdominal infection. In PVT group of 15 patients who did not receive anticoagulation, malignancy was most common cause, either from primary hepatocellular carcinoma or hepatocellular carcinoma with metastasis (► **Table 1**).

The group who received anticoagulation had a lower proportion of patients with hypertension and history of

Table 1 Demographic data

	Overall	Anticoagulation	No anticoagulation
Count	30	15 (50.0%)	15 (50.0%)
Age: mean (y)	60.8	55.6	66.0
Range (y)	30–91	30–77	45–91
Gender			
Male	19 (63.3%)	11 (86.7%)	8 (53.3%)
Female	11 (36.7%)	4 (26.7%)	7 (46.7%)
Ethnicity			
Chinese	21 (70.0%)	10 (66.7%)	11 (73.3%)
Malay	2 (6.7%)	0 (0.0%)	2 (13.3%)
Indian	2 (6.7%)	1 (6.7%)	1 (6.7%)
Others	5 (16.7%)	4 (26.7%)	1 (6.7%)
Malignancy	13 (43.4%)	6 (40.0%)	7 (46.7%)
Infection	13 (43.4%)	8 (53.3%)	5 (33.3%)
Cirrhosis	4 (13.3%)	2 (13.3%)	2 (13.3%)
Comorbidities			
Diabetes mellitus	8 (26.7%)	4	4
Hypertension	14 (46.7%)	9	5
Previous thrombotic events	4 (13.3%)	3	1
Hypercoagulable state	5 (16.7%)	2	3

previous thrombotic events compared with those who did not receive anticoagulation. Incidence of diabetes was the same in both groups (► **Table 1**).

Investigations of PVT occlusion extent, presence of intestinal ischemia, portal hypertension, portal cholangiopathy, and thrombocytopenia were performed prior to initiation of treatment. Out of 15 patients in both arms (anticoagulation vs. no anticoagulation), complete luminal occlusion was seen in 10 out of 15 patients in each group and partial occlusion was seen in 5 out of 15 patients in each group. Involvement of other veins such as superior mesenteric, inferior mesenteric, or splenic vein is shown in ► **Table 2**. Single case of intestinal ischemia was seen in patient who did not receive anticoagulation. Incidence of portal hypertension was seen in two patients in anticoagulation group and one patient in the other group.

Of the 15 patients who received anticoagulation, there was complete resolution of thrombus in 5 (33.3%), partial

Table 2 Investigations and complications: overall

	Overall	Anticoagulation	No anticoagulation
Total	30	15 (50.0%)	15 (50.0%)
Radiology scan			
PVT occlusion: complete	20 (66.7%)	10 (66.7%)	10 (66.7%)
PVT occlusion: partial	10 (33.3%)	5 (33.3%)	5 (33.3%)
Additional occlusion: 1 vein (SMV, IMV, SV)	8	5	3
Additional occlusion: 2 veins (SMV, IMV, SV)	7	4	3
Additional occlusion: 3 veins (SMV, IMV, SV)	2	2	0
Intestinal ischemia	1	0	1
Portal hypertension	3	2	1
Portal cholangiopathy	0	0	0
Thrombocytopenia (platelet <100)	7	4	3

Abbreviations: IMV, inferior mesenteric vein; SMV, superior mesenteric vein; SV, splenic vein.

resolution in 1 (6.7%), and no resolution in 9 (60.0%). Of these 15 patients, there was bleeding in 3 (20.0%), there was no recurrence in 9 (60.0%), and 3 (20.0%) died during the period of follow-up. Of the 15 patients who did not receive anticoagulation, there was complete resolution of thrombus in 2 (13.3%), partial resolution in 0 (0.0%), and no resolution in 13 (86.7%). Of these 15 patients, there was bleeding in 0 (0%), there was recurrence in 2 (13.3%), and 6 (40.0%) died during the period of follow-up.

Out of the 13 patients with malignancy, 6 patients received anticoagulation and 7 patients did not receive anticoagulation, the mortality rate was 4 (66.7%) out of 6 in anticoagulation group and 4 (57.1%) out of 7 in group who did not receive anticoagulation. However, the survival time in days (mean) was 291 days (range of 22–981) in anticoagulation group and 90 days (range of 6–219) in group who did not receive anticoagulation. Out of the 13 patients with infections, 8 patients received anticoagulation and 5 patients did not receive anticoagulation. There was no mortality rate in any

groups; however, there was recurrence in one out of five patients in group who did not receive anticoagulation and no recurrence in the group who received anticoagulation. Out of the four patients with infections, two patients received anticoagulation and two patients did not receive anticoagulation. There was no mortality rate in anticoagulation group compared with 50% mortality in the group which did not receive anticoagulation. There was recurrence in one out of two patients in patient who did not receive anticoagulation.

Anticoagulation therapies of low-molecular-weight heparin (LMWH) or a combination of LMWH and warfarin were used during the 5-year period. Of the 15 patients who received anticoagulation, 7 (46.7%) received LMWH, and 8 (53.3%) received the combination of LMWH and warfarin. Mean target international normalized ratio (INR) in patients receiving warfarin was 1.67, with a range of 1 to 3.3. Only three of the eight patients were within this target INR for a period of 60% or more. Mean duration of anticoagulation use was 66 days, with a range of 2 to 243 days (► **Table 3**).

Table 3 Use of anticoagulation

	Overall	Malignancy	Infection	Cirrhosis
Overall	15	6	9	3
Regime: LMWH	7 (46.7%)	5 (83.3%)	4 (44.4%)	1 (33.3%)
Regime: LMWH + warfarin	8 (53.3%)	1 (16.7%)	5 (55.6%)	2 (66.7%)
Target INR: mean	1.67	2.65	1.52	2.21
Target INR: range	1–3.3	1.99–3.31 ^a	1–2.06	2.01–2.4
INR within therapeutic range 60% of the time	3	0	2	3
Anticoagulation duration: mean duration (d)	66	75	61	27
Anticoagulation duration: range (d)	2–243	11–122	2–243	10–45

Abbreviations: INR, international normalized ratio; LMWH, low-molecular-weight heparin.

^aDifficult to titrate due to hepatocellular carcinoma.

Note: LMWH or a combination of LMWH and warfarin was used in patients. No novel anticoagulation agents, such as rivaroxaban or dabigatran, were used. Target INR for patients on LMWH and warfarin therapy recorded.

Discussion

The efficacy of anticoagulant therapy in the setting of PVT has been well documented in the previous studies. In a 2015 meta-analysis of 16 observational studies on cirrhotic patients with PVT, Qi et al determined a pool rate, the rates of recanalization with anticoagulation, was significantly higher in the anticoagulated group than in the nonanticoagulated group (odds ratio = 4.16, 95% confidence interval [CI] = 1.88–9.20, $p = 0.0004$).⁵ Our data suggest similar results.

Increased mortality rates were identified in PVT patients with cirrhosis.⁶ A study by Turnes et al suggests a rate of 87% for 5-year survival of patients receiving anticoagulation therapy.⁷ From our data, mortality rates were lower in PVT patients who received anticoagulation. Mean survival duration was increased from 90 to 291 days from use of anticoagulants in patients with PVT and malignancy.

Increased age in PVT is also known to be associated with increased mortality—with a hazard ratio of 1.02 (95% CI).⁶ In our study group, patients who received anticoagulation were 10.4 years younger compared with those who did not receive anticoagulation. This may account for decreased mortality rates seen in patients on anticoagulation in our study. The effects of thrombus extent have been described in the previous study. Greater the extent, poorer the outcomes.⁸ In our study, the complete and partial occlusions were similar in both groups.

In a study by Condat et al, 84 of 136 patients were treated with anticoagulant therapy, a documented incidence rate of gastrointestinal bleeding was recorded as 12.5 per 100 patient-years (95% CI, 10–15).³ The study concluded by stating that the risk of thrombosis is currently as clinically significant as the risk of bleeding—with the benefit–risk ratio favoring the use of anticoagulant therapy. In our study, there was increase bleeding risk of patients receiving anticoagulation.

A decrease in recurrence and complete thrombosis and increase in recanalization rates are seen with the use of anticoagulation.^{9–11} Similar findings were seen with our study.

The use of anticoagulation in noncirrhotic patients with acute PVT, anticoagulation therapy is beneficial.^{12–16} Thrombolysis has also been used in extensive mesenteric vein and PVT.¹³ In our study, no patients received thrombolysis. It is also known that use of anticoagulation therapy to treat PVT in the setting of cirrhosis should be done after a thorough assessment of the risk of bleeding against the risk of rethrombosis.¹⁷

All patients with PVT should be investigated for thrombophilic conditions as possible causes. Cirrhosis is considered as the main cause of PVT and is a fluctuant disease. Treatment with low-weight heparin should be considered in these patients.¹⁸ Investigating for thrombophilia is not a routine practice in our center.

Anticoagulants are a safe treatment for PVT and partial or complete recanalization is seen in many patients.¹⁹ In our study, anticoagulation increased the bleeding risk by 20%. The early initiation of anticoagulation in patients of superior mesenteric vein thrombosis combined with PVT could minimize the serious complication such as peritonitis due to bowel necrosis required immediate exploratory laparotomy.²⁰ Our

understanding of the etiology, natural history, and treatment options for extrahepatic PVT have improved over the past few years. The recognition that multiple risk factors, including inherited and acquired thrombophilic predispositions, are involved in the majority of cases merits a methodical search for these, as their identification may influence management.²¹ Rare case of massive upper gastrointestinal bleeding due to pancreatic pseudocyst rupture into the duodenum, which developed during anticoagulation therapy for acute pancreatitis associated with PVT has been reported.²² Thus, bleeding risk on anticoagulation needs to be monitored closely in these patients.

Our study shows that over 5-year period, treatment of PVT with anticoagulation irrespective of cause, there is a benefit in anticoagulation therapy though there is slight increase in bleeding risk in these patients with overall improvement in mortality.

However, the study has the following limitations:

1. This is retrospective data analysis.
2. The sample size is small. This is due to the fact that PVT is not very common condition seen in our population.

Conclusion

Anticoagulation is effective in PVT. It reduces mortality by 50%, helps in resolution of thrombus, and lower rate of recurrence when compared with those with no anticoagulation. The rate of recanalization with anticoagulation is three times higher compared with ones who do not receive anticoagulation. However, anticoagulation is associated with three times increased risk of bleeding and should be used with caution in patients with increased bleeding risk.

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