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Original Article

Non tumoral portal vein thrombosis during cirrhosis: Should anticoagulation be proposed?

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Abstract

Background:

Portal vein thrombosis (PVT) is considered as infrequent and pejorative event in cirrhosis. Up to date, many questions remain about therapeutic management.

Aim:

The objectives of this study were to assess the impact of the PVT on the progression of liver disease, to review the indications for anticoagulation and its repercussions.

Materials and methods:

A case-control study was conducted over a period of 12 years (2002-2013). It included 484 cases of cirrhosis. Among these patients, 41 had non tumoral portal vein thrombosis (case group). The control group included the remaining 443 patients.

Results:

In our study, there was no impact of PVT on the natural history of cirrhosis both in terms of complications or survival. Only the early introduction of anticoagulant therapy was associated with a re-permeabilization of portal vein at one year (OR1.6; 95% CI [1.10-2.01]). Prolonged anticoagulation was inversely correlated with recurrent PVT after treatment. However, obtaining a portal vein re-permeabilization was not correlated to a significant gain in terms of prevention of complication related to cirrhosis and survival.

Conclusions:

results suggest that portal vein thrombosis in patients with cirrhosis is not a formal indication for anticoagulant therapy. It should be reserved for candidates of liver transplantation, those with an extension of the PVT to mesenteric vessels or with severe prothrombotic status.

Key words:

portal vein thrombosis, cirrhosis, anticoagulation.

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Introduction:

Non tumoral Portal vein thrombosis (PVT) during cirrhosis is considered as an uncommon and pejorative event [1]. The causes of PVT belong usually to local and / or general factors, including cirrhosis [2]. However, the impact of PVT on the cirrhosis mortality and liver disease progression remains questionable. Therapeutic management of PVT remains difficult due to the lack of national and international guidelines and the absence of objective tools for benefit -risk balance assessment.

Patients and methods:

In our work, we first investigated the indications of anticoagulants in a group of cirrhotic patients with non-tumoral PVT. We studied efficiency as well as complications occurring during anticoagulation. In a second step, we studied the effect of PVT on the progression of liver disease and the impact of the re-permeabilization on survival.

A case-control study including all adults with cirrhosis hospitalized in the Gastroenterology department of the Habib Thameur Hospital during 12 years (January 2002 May 2013) was performed.

The case group consisted in patients with:

-Cirrhosis diagnosed most often on the association of clinical, biological, morphological and endoscopic arguments;

-Acute or chronic PVT diagnosed by Doppler ultrasound or by tomodensitometry with intravenous contrast;

-A minimum follow-up of 3 months;

The control group was composed of patients with the same inclusion criteria but without PVT.

Patients with a history of neoplastic pathology in remission, or hepatocellular carcinoma (HCC) were not included in our study.

Exclusion criteria were:

-Patients who received anticoagulation for another indication than the PVT before their inclusion;

-Patients with a follow-up of less than 3 months;

- patients who developed a HCC within a period of 6 months next to PVT diagnosis.

The diagnosis of PVT was made by ultrasound coupled with the Doppler or by a tomodensitometry with contrast injection. The main objective of imaging was to establish the diagnosis of PVT, to determine its partial or total character, to specify its extension in particular to splanchnic vessels and to eliminate mesenteric venous ischemia

Imaging aimed also to eliminate neoplastic causes for PVT as well as septic pylephlebitis.

Endoscopic monitoring was performed for all patients according to the last Baveno VI guidelines. Primary or secondary prophylaxis of gastrointestinal bleeding was established according to endoscopic data. Each time a treatment for PVT has been established, the following data have been specified: the therapeutic indication, the modalities of the treatment, the delay in initiating the treatment with respect to the diagnosis of PVT and its duration. Clinical and radiological follow-up of the patients were recorded.

We studied the spontaneous radiological evolution or under anticoagulant treatment, as well as the evolution of the hepatic function according to the re-permeabilization or not of the portal vein. When a radiological follow-up was carried out during the year following the diagnosis of PVT, the reversal of the PVT was qualified as total, partial or absent.

The success of the treatment instituted was confirmed by a total re-permeabilization of the portal vein.

Hemorrhagic complications (digestive or extra-digestive) under anti-coagulation were recorded, as well as their time of appearance and their evolution. At the end of the study survival was compared in both groups.

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The statistical analysis was carried out by SPSS.21.

The averages were compared using the Student T test and the Mann and Whitney nonparametric test. The comparison of percentages on independent series was carried out by the Pearson Chi-square test and the Fisher test. The survival analysis was performed according to the Kaplan-Meier method. The analysis of the prognostic factors was based on the Log-Rank test for the univariate analysis. A logistic regression according to the Cox model was used for the multivariate analysis. A p value was considered statistically significant if <0.05.

Results:

A total of 548 cirrhotic patients hospitalized in the department were recorded. In total, 484 cirrhotic patients have no HCC, in which 41 cases with PVT and 443 controls were included. The prevalence of non tumoral PVT in cirrhosis was thus of 8.5% in our study. Twenty-three patients (56.1%) received anticoagulant therapy.

The indications of anticoagulation were:

- Extension of the PVT to the mesenteric vessels with or without signs of intestinal ischemia: 12 patients (one died before the beginning of anticoagulation).

- Severe prothrombotic status (protein C deficiency, anti-thrombin III deficiency): 3 patients (1 case of one extension of the PVT to the mesenteric veins).

- When the benefit-risk balance was in favor of anticoagulant treatment: 10 patients with mild cirrhosis (CHILD A and B7 score).

All patients treated (n=23) received Antivitamin K (AVK)-based anticoagulation. The 11 patients with extension of the PVT to the mesenteric vessels with or without signs of intestinal ischemia as well as the 2 patients with a severe prothrombotic status initially received an anticoagulant treatment based on low molecular weight heparin (LMWH) then relayed by the AVK.

The average time to introduce AVK was 2.6 days. LMWH was introduced immediately in case of mesenteric ischemia. The mean duration of anticoagulation was 8.65 months (1-24).

The average duration of follow-up was 26.4 months (1-120). Seven patients had no radiological control of their PVT. For the others, Doppler monitoring was performed every 3 to 6 months.

Among the 34 patients followed over 3 months, re-permeabilization was obtained in 19 cases (55.8%). It was total in 29% of cases. In patients with anticoagulant therapy (n=23), portal re-permeabilization was obtained in 69.5% (n=16) and was total in 10 (43.5%). In the 11 untreated patients, re-permeabilization was obtained in only 27.2% (n=3) and no case of total re-permeabilization of the portal vein was noted. The difference was statistically significant (p=0.025) (Figure 1). In the treated group re-permeabilization was obtained within a year in 79% of cases. The average duration of re-permeabilization was 7.9 months. All patients treated for 12 months (n=10) had complete re-permeabilization of their portal vein. On the other hand, in 9 patients treated for less than 6 months, a re-permeabilization was obtained in 44.4% of the cases (n=4), and a PVT reappeared in one case. (Figure 2)

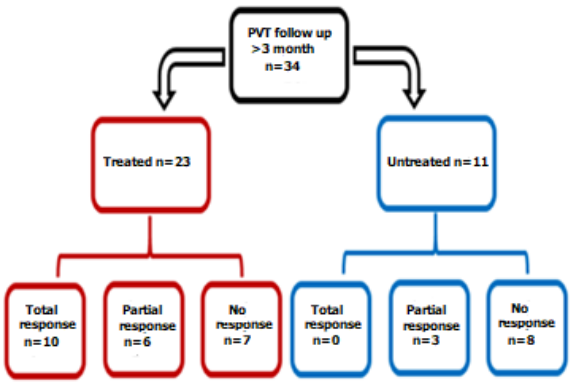

Figure 1: Evaluation of the re-permeabilization of the portal vein with vs without anticoagulation

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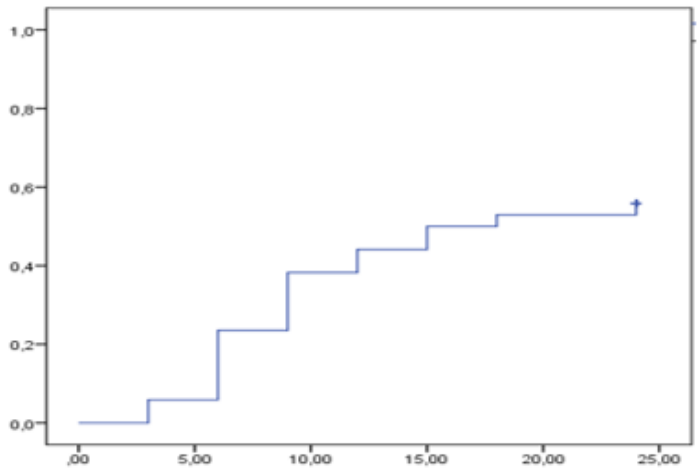

Figure 2: time to PVT re-permeabilization (months)

During the follow-up, 2 patients presented extra-digestive hemorrhage (epistaxis) and one case of gastrointestinal hemorrhage due to varicose rupture. Two cases of gastrointestinal hemorrhage were recorded in untreated patients (6.5%).

Eleven (32.3%) patients developed a non-hemorrhagic complication following the diagnosis of PVT including 2 cases of refractory ascites, 5 cases of hepatic encephalopathy and 4 cases of spontaneous bacterial peritonitis. Overall survival at 1 year and 2 years were respectively 68.3% and 34.1%.

The median survival was 24 months. At two years, 4 of the 27 patients who died were in the successful group. The remaining 23 were among patients with failure or absence of the treatment. Liver disease progression was the cause for all the patients of the treated group and for 20 patients from the other group.

Thus, at two years, the overall mortality rates in the two groups were 40% and 74.2% respectively. If only specific mortality is considered, the respective rates increase to 40% and 64.5%.

The introduction of an anticoagulant treatment but especially its early character (within 30 days after the diagnosis of the PVT) represented decisive factors in the obtaining of a portal re-permeabilization in our study. Thus, 3 factors appeared to be correlate with portal re-permeabilization in univariate analysis: initiation of anticoagulant therapy ($p = 0.025$), initiation of treatment within one month after diagnosis of PVT ($p = 0.005$), and a partial PVT ($p = 0.027$). However, in multivariate analysis, only the rapid onset of treatment within 7 days was significantly correlated with re-permeabilization of the portal vein with an OR of 1.6; 95% CI [1.10-2.01] (Table 1)

The introduction of effective anticoagulant therapy (with complete portal re-permeabilization) does not seem to have any effect on the evolution of cirrhosis. Thus, there was no significant difference between the two groups of patients in case of regression or persistence of PVT concerning complications such as spontaneous bacterial peritonitis ($p = 0.912$), refractory ascites ($p = 0.263$), hepatic encephalopathy ($p = 0.748$), gastrointestinal hemorrhage ($p = 0.421$). Moreover, the overall rate of complications was comparable between the two groups ($p = 0.452$).

Twenty-four liver-related deaths occurred in the first two years, of which 4 were successfully treated for the PVT. There was no significant difference between the patients in whom total permeability was obtained comparing specific mortality rate at 1 year ($p = 0.282$) and at 2 years ($p = 0.171$) (Figure 3).

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Variable	*p (univariate analysis)*	*p (multivariate analysis)*
Treatment	0.025	NS
Partial PVT	0.027	NS
Initiation of the treatment within 30 days	0.005	**0.038; OR=1.6 [1.1 – 2.01]**

Table 1: Predictive factors of re-permeabilization of the portal vein

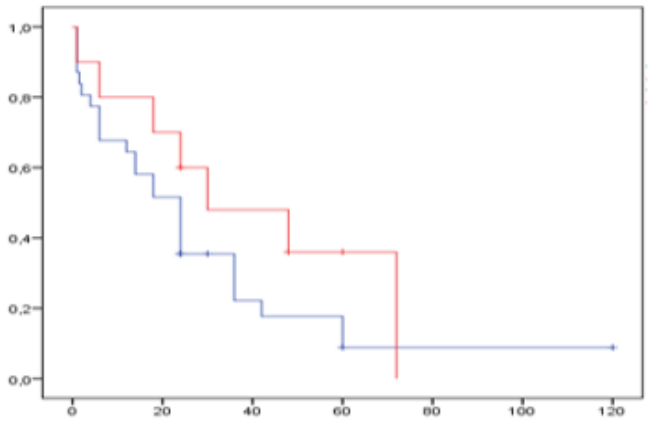

Figure 3: Survival after total re-permeabilization obtained (blue curve) vs not obtained (red curve)

Three hemorrhagic events (2 cases of epistaxis and 1 case of gastrointestinal hemorrhage due to varicose rupture) occurred under AVK. The mean time to bleeding complication was 1.7 months and the 3 hemorrhagic events occurred during the first quarter of treatment. Two cases of gastrointestinal hemorrhage occurred in untreated patients (6.5%). The patients presenting hemorrhagic events were minor and the AVK treatment was not discontinued.

Discussion:

The lack of consensual guidelines for the management of PVT in cirrhotic patients is may be due to the difficult assessment its impact on the cirrhosis natural history. However, the basic concept of any proposed treatment is the safety and the positive impact on the evolution of the liver disease [3].

Regarding primary prevention, Villa et al demonstrated that the use of Enoxaparin 4000 IU once daily for 48 weeks in CHILD B7-C10 cirrhotic patients prevented both the onset of PVT and the decompensation of the cirrhosis (p <0,0001 compared to controls) and improved mortality (p=0.02) with a benefit maintained between 2 and 4 years [4]. This suggests the action of anticoagulation both on PVT and progression of hepatopathy. Thus, alteration of hepatic and / or intestinal microcirculation seems to be under the direct influence of coagulation abnormalities.

Previously in the literature; 6 studies including a total of 199 patients treated this topic (Table 2).

Our results about the effectiveness of anticoagulation for PVT in cirrhotic patients are limited. Heterogeneous data; the lack of precision in the assessment of the PVT extension; and unavoidable selection bias in some situations decreased the specificity of the analysis. However, the tolerance and the absence of interference with the mortality due to digestive bleeding are well demonstrated now. This was also remarkable in many other studies [4,6,9,10]. For spontaneous or induced (secondary to paracentesis for example) extra-digestive hemorrhage, the only established risk factor is severe thrombocytopenia <50,000 / ml [5-10].

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	Type of study	n (controls)	Severity of the cirrhosis	Type and duration of anticoagulation	Type of PVT (patial/total)	Re-permeabilization (total/partial)	Stabilization/ progression	Bleeding complications
Werner and al (3)	Retrospective	28	MELD 7-29	Warfarin 10 months	-	11 (39.3%) / 17 (60.7%)	10(53%)/1(5%)	1 vaginal
Villa and al (4)	Controlled randomized essay	34 (36)	Child Pugh 7-10	Enoxaparin 12 to 24 months	Primary prevention	-	7/0	4 (2 digestive)
Delgado and al (6)	Retrospective	55	MELD 12.8	Warfarin Enoxaparin 6.8 months	41 (75%) / 14 (25%)	25 (45%) / 30 (55%)	0/0	10 (8 digestive)
Amiltrano and al (7)	Prospective	28	-	Enoxaparin 6months	23 (82%) / 5 (18%)	21 (75%) / 5 (18%)	0 (treated)/10(28%) untreated	0
Senzolo and al (12)	Cases, controlled, Prospective	33 (21)	MELD 12.6	Nadraparin 6 months	24 (69%) / 11 (31%)	12 (34%)/ 9 (26%)	0/2(7%)	4 (1 digestive)
Francoz and al (16)	Cases, controlled, Prospective	19 (10)	MELD 12.8	Warfarin 8 months	18 (95%) / 1 (5%)	8 (42%) / 0	7(20%)/5(15%)	1 (after band ligation)
Our study	Cases, controlled, retrospective	41 (434)	MELD 15.9	Antivitamin K 8.7months	30 (73%) / 11 (27%)	Treated (n=23) 10/6 Untreated (n=11) 0/3	3/5	3 (1 digestive)

Table 2: review of previous reports regarding anticoagulation for PVT in cirrhotic patients

About the curative treatment, data from the literature agreed with our results for total or partial re-permeabilization (rates are 40% and 15% respectively) [11]. Complete re-permeabilization of the portal vein is obtained for almost all patients with treatment duration >1 year [7,12] early discontinued treatment is associated with recurrence in 25% of cases [6]. Some other authors support the fact that 40% of the PVT decreases in size spontaneously. The only predictive factor of re-permeabilization under anticoagulation is, such as found in our study, the early introduction of anticoagulant. The relationship between permeability and complications, described in some series, was not confirmed by comparative studies [13]. Many new oral anticoagulants have been commercialized, Rivaroxaban® proved its efficacy and safety [14,15]. These molecules have many advantages such as easy route of administration and the absence of interaction with the INR and MELD score. Therefore, no continuous monitoring is required. Their disadvantage includes the absence of antidote and frequent drug interactions.

Finally, in light of the above publications and our results, anticoagulant therapy is recommended in the following situations:

1. In patients with advanced cirrhosis who are considered for short-term or medium-term therapy, an anticoagulant treatment, preceded by a preventive treatment of gastrointestinal bleeding should be proposed. An easier access for hepatic transplantation and the improvement of post-operative survival are rational behind this recommendation. The aim is to solve the portal obstruction or at least to limit its extension.

2. In the presence of a PVT extended to the mesenteric vessels with or without signs of intestinal ischemia. The aim of the treatment is to prevent mesenteric infarction.

3. A strong prothrombotic status associated with PVT in a cirrhotic patient is also an indication for anticoagulant therapy alone or in combination with TIPS.

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Conclusions:

Our study showed that untreated PVT has no impact on the progression of cirrhosis neither on the overall survival. the only complication correlated with the portal obstruction was the gastrointestinal hemorrhage with a higher incidence and a more complicated management. From a therapeutic point of view, only the early introduction of anticoagulant therapy was associated with portal re-permeabilization at one year and prolonged anticoagulation was inversely correlated with recurrence of PVT after discontinuation of treatment

Conflict of interest: none

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