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BEYOND THE GUIDELINES: ANTICOAGULANT TREATMENT OF PATIENTS WITH RECENT PORTAL VEIN THROMBOSIS IN THE SETTING OF LIVER CIRRHOSIS

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Abstract

Portal vein thrombosis, in the clinical setting of liver cirrhosis, is a complication which increases mortality rate by leading to specific complications. Its presence also serves as a negative prognostic factor for these patients. Specialized literature, although rich in papers on this subject, presents loose and sometimes contradictory information regarding its prognosis and specific treatment. This paper brings into discussion the issue of recent portal vein thrombosis in cirrhotic patients, with emphasis on indications for initiation of anticoagulant therapy and the optimal drug of choice. It also highlights the utility of using correct terminology for facilitating clinical approach of guideline recommendations as well as increasing the quality of published scientific papers.

The coagulation homeostasis of the cirrhotic patient presents many particularities that can make the optimal therapeutic choice extremely difficult when portal vein thrombosis is established. Absence of randomized clinical trials and lack of consensus regarding anticoagulant treatment in these patients leaves it up to the clinician to decide when and what anticoagulant to use. Analysis of the newest guidelines and recent meta-analysis made it possible to identify the right context for initiating therapy with the most used anticoagulants currently: low molecular weight heparin, vitamin K antagonists and direct oral anticoagulants.

Keywords: *portal vein thrombosis, liver cirrhosis, anticoagulant treatment.*

Rezumat

Tromboza venei porte, în contextul cirozei hepatice, este o complicație ce crește mortalitatea, un factor de prognostic negativ, care atrage după sine complicații specifice. Literatura de specialitate, deși deloc pauperă în ceea ce privește abundența lucrărilor referitoare la acest



subiect, prezintă informații laxe și, uneori, contradictorii referitoare la prognosticul și tratamentul specific al acesteia. Lucrarea de față aduce în discuție problematica trombozei de venă portă la pacientul cirotic, cu accent asupra indicațiilor de inițiere a terapiei anticoagulante și a alegerii clasei optime de anticoagulant. De asemenea, este subliniată utilitatea folosirii terminologiei corecte pentru a crește aplicabilitatea clinică a recomandărilor de ghid, precum și a calității materialelor științifice publicate.

Homeostazia coagulării pacientului cirotic prezintă numeroase particularități care pot face extrem de dificilă alegerea sancțiunii terapeutice optime atunci când se instalează tromboza de venă portă. Absența unor studii clinice randomizate și lipsa de consens în ceea ce privește tratamentul anticoagulant la pacientul cirotic cu tromboză a venei porte lasă la latitudinea clinicianului stabilirea indicației de anticoagulare și a medicamentului de elecție. Consultarea ghidurilor de actualitate și a unor meta-analize recente a permis evaluarea contextelor potrivite pentru inițierea celor mai folosite clase de anticoagulante în practica medicală: heparina cu greutate moleculară mică, anticumarinicele și anticoagulantele orale directe.

Cuvinte cheie: *tromboza de vena porta, ciroza hepatica, tratament anticoagulant.*

Introduction

The portal vein, formed by the confluence of the splenic and superior mesenteric veins, plays an important role in the pathophysiology and natural evolution of liver cirrhosis. In the hepatic hilum it divides into a left and a right branch, which together provide up to 75% of the liver blood flow[1]. Venous patency and portal flow pressures are elements that greatly influence the course of the disease and the occurrence of possibly life-threatening complications of liver cirrhosis: esophageal varices, hepatic encephalopathy, ascites and spontaneous bacterial peritonitis. Proper identification and correct nomenclature of the different types of portal vein thromboses are extremely important for achieving standardized terminology (Table 1) in both studies and medical practice. Two types of thrombosis have been identified based on the clinical features and the moment of discovery: recent (previously called acute) and chronic. Portal vein thrombosis is considered chronic 6 months after diagnosis or in a patient with unknown onset of portal vein thrombosis with changes such as cavernomatous transformation or collateral circulation. Recent

portal vein thrombosis is used to describe cases with proven sudden onset, less than 6 months, or when cavernomatous changes and collateral circulation are absent, with unknown onset. The term "acute thrombosis" is used in cases with recent onset and clinical features, but since most of the cases are clinically silent, the latest guidelines recommend using the term "recent thrombosis". The 6 months threshold was established by following the time required for the occurrence of chronic thrombosis changes[2].

Portal vein thrombosis can also occur in various other pathologies (e.g. tumor invasion, paraneoplastic syndromes, blood dyscrasias). A targeted approach and an optimal, individual treatment choice for each patient are required.

This paper will highlight the issues regarding recent portal vein thrombosis in patients with liver cirrhosis[3].

Coagulation balance in patients with liver cirrhosis

Coagulation homeostasis in cirrhotic patients represents an important challenge for clinicians. The mechanisms involved are multiple and complex. Reduced hepatic synthesis of coagulation factors and secondary thrombocytopenia caused by portal hypertension-induced splenomegaly generates a bleeding risk. However, there is a decrease in the synthesis of endogenous anticoagulants - protein S, protein C and antithrombin. VIIIth and von Willebrand factors have increased serum levels, both through reduced hepatic clearance and increased endothelium synthesis, which generates a thrombosis risk. Moreover, simply monitoring the coagulation balance becomes difficult in the case of patients with liver cirrhosis. Two of the most commonly used hemostasis tests, INR value and platelet count, are imprecise in assessing these patients[4]. INR was validated only for patients with normal liver function. Studies have shown up to 29% variability of mean values of INR in cirrhotic patients[5]. For this reason, a new test called hepatic INR was proposed. However, the test is not widely available and is unlikely to provide a significant clinical advantage, given the limitations of prothrombin time as a predictor of bleeding risk or thrombotic events[6].

Similarly, some studies suggest that in patients with compensated liver cirrhosis, a platelet count even below 50x10^3/mm^3 does not associate with an increased number of hemorrhagic events[4].

Another important factor is the degree of liver disease decompensation. The current tendency is to consider compensated and decompensated cirrhosis as two distinct entities with different risks and different therapeutic options[4].

Portal vein thrombosis is an integral part of a vicious cycle in which it is either induced by cirrhosis decompensation or it has an insidious onset and causes complications that lead to decompensation.

Predictive risk factors of portal vein thrombosis have been identified[7]. Table 2 illustrates them in summary.

Diagnostic

Portal vein thrombosis is caused by thrombus formation in the intrahepatic portal branches or the extrahepatic portal vein. This can be complete, with occlusive thrombus, or partial, non-occlusive, with a thrombus that only partially occupies the lumen of the vein. In dramatic cases, the thrombus can extend to the portal confluents, occupying the splenic vein or superior mesenteric vein.



Internal Medicine

General Reviews

About half of the cases are incidentally diagnosed during screening imaging investigations for hepatocellular carcinoma. In the PRO-LIVER study 43% of the cases of recent portal vein thrombosis were asymptomatic[8].

The clinical picture, extremely variable and non-specific, may include symptoms like abdominal pain of varying intensity, nausea and vomiting. In the cirrhotic patient, acute portal vein thrombosis may be accompanied by signs and symptoms of vascular complications of decompensated cirrhosis: variceal bleeding or ascites[9]. Severe cases in which the thrombus extends to the superior mesenteric vein have a noisier clinical presentation with abdominal distension, colicky abdominal pain and diarrhea. Thrombosis of the superior mesenteric vein can lead to intestinal wall edema that causes ischemia and entero-mesenteric infarction.

The onset of fever, ascites, peritoneal irritation, leukocytosis and elevated serum lactate levels raises suspicion of acute mesenteric ischemia associated with portal vein thrombosis[6] and requires more complex imaging investigations.

Diagnosis of recent portal vein thrombosis is based on imaging. Abdominal Doppler ultrasound is non-invasive and has a very wide availability, thus being the most used diagnostic test, with 89-93% sensibility and 92-93% specificity.

In addition to direct visualization of the thrombus as hypoechoic material (fresh thrombus) (Figure 1) or intraluminal hyperechoic material (old thrombus) and absence of Doppler flow, indirect signs (very important in hyperacute thrombosis) are portal vein distension over 13 millimeters, without respiratory variation[3].

For acute or recent portal vein thrombosis there is also noted the absence of adaptive changes like collateral circulation or portal cavernoma (Figure 2), which are characteristics of chronic thrombosis.

Contrast-enhanced computed tomography and MRI are highly sensitive and specific imaging investigations, with the added advantage of allowing visualization of the entire spleno-portal circulation, but may be difficult to obtain in decompensated patients and are less available.

Treatment

There is a lack of consensus regarding anticoagulant treatment in cirrhotic patients with acute portal vein thrombosis. On the one hand, there is the increased variability of these patients' bio-clinical presentation which depends on the Child-Pugh class of cirrhosis, the presence of decompensation and its nature, each patient having a different bleeding risk. On the other hand, the absence of randomized clinical trials and a percentage

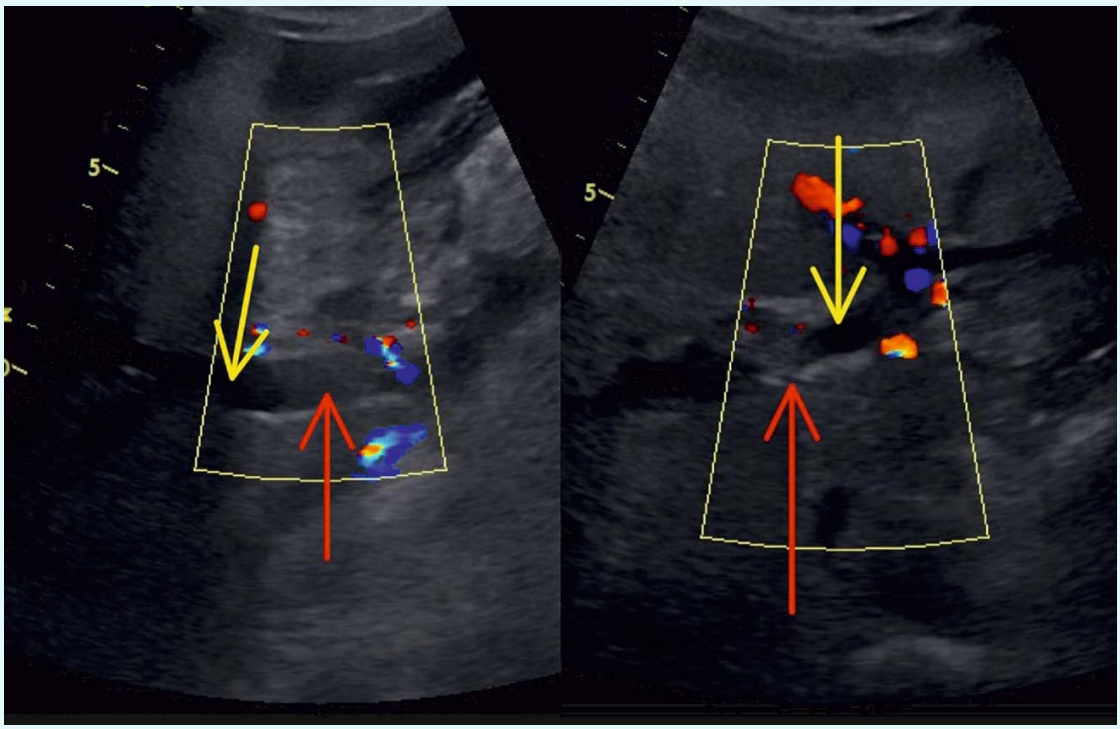


Figure 1. *Completely occlusive thrombus in the portal vein. Complete absence of Doppler flow (yellow arrows), increased diameter of the vein and the presence of hyperechoic homogeneous intraluminal material (red arrows). Chronic portal vein thrombosis elements are not present (images from the personal library of Dr. Dan Victor Spătaru)*

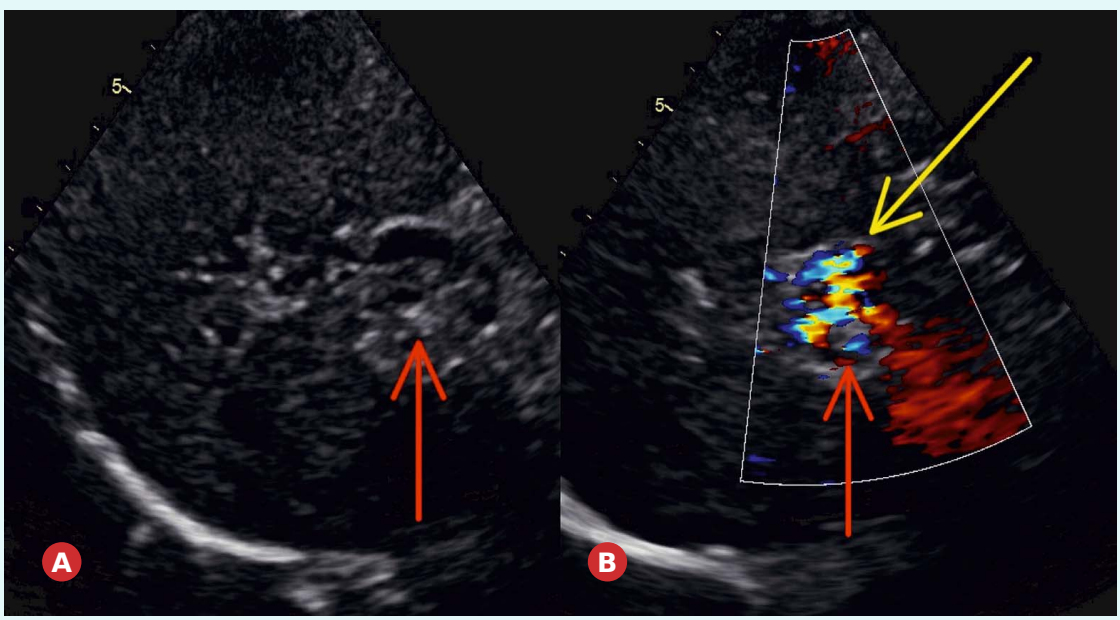


Figure 2. *Portal cavernoma. Absence of the portal vein lumen with hyperechoic completely occlusive thrombus (a - red arrow) surrounded by hyperdynamic collateral circulation (b - Doppler examination - yellow arrow), classic chronic portal vein thrombosis findings (images from the personal library of Dr. Dan Victor Spătaru)*

Criteria	Terminology	Definition
Duration	Recent	Less than 6 months
	Acute	Less than 6 months+clinical features
	Chronic	More than 6 months
Percentage of lumen occlusion	Minimally occlusive	<50% lumen occlusion
	Partially occlusive	>50% lumen occlusion
	Completely occlusive	No visible lumen
	Cavernomatous changes	No visible lumen + portosystemic collateral circulation
Treatment response	Regressive	Thrombus shrinking
	Stable	Without changes
	Progressive	Thrombus increase

Table 7. *Correlations between cholinesterase, albumin and INR in all patients*

- old age
- Child-Pugh class B or C
- decrease in portal vein flow velocity (<15 cm/s)
- decrease in prothrombin time
- esophageal varices ≥ grade 2
- concomitant presence of hepatocellular carcinoma
- history of portal thrombosis or digestive hemorrhage

Table 2. *Predictive factors of portal vein thrombosis(7)*

of these patients being frail determined the absence of a firm therapeutic algorithm suitable for all clinical contexts.

Several retrospective studies and meta-analyses have evaluated the effectiveness of different anticoagulants by tracking the degree of portal vein repermeabilization and bleeding complications under treatment. There were also some "watch and wait" cases that were analyzed, following the evolution of patients without anticoagulation.

A meta-analysis comprising 8 clinical trials including 353 patients, shows spontaneous repermeabilization without anticoagulant therapy in 42% of cases of acute portal vein thrombosis. However, the same meta-analysis shows repermeabilization in 71% of the cases that benefited from anticoagulant treatment[10].

Current guidelines recommend initiation of anticoagulation therapy in patients with recent, complete thrombosis of the portal vein, ones with thrombosis of the superior mesenteric vein or extension of the thrombus towards the superior mesenteric vein and also in patients with chronic thrombosis and thrombophilia or extension of the thrombus towards the portal branches[2], after careful evaluation of the bleeding risk and the establishment of gastrointestinal bleeding prophylaxis measures. Absolute contraindications to anticoagulant treatment are the same as in patients without liver disease: clinically significant active bleeding, severe thrombocytopenia (below 50,000/µL), major trauma, invasive procedures or interventions that contraindicate anticoagulation, etc.

Asymptomatic cases of recent partial thrombosis with non-obstructive thrombus and no extension to the portal tributary veins that are diagnosed incidentally can, initially, only be monitored. The expectant attitude may also be appropriate for patients with severely decompensated cirrhosis and/or severe alteration of coagulation tests, even if they cannot accurately identify the patient's bleeding risk profile[9]. This therapeutic attitude provides time for the clinician to perform a more complex biological assessment of the patient and to provide supportive treatment, with an ulterior reassessment of the hemorrhagic risk and ultrasonographic monitoring the evolution of the thrombus, in order to determine the optimal moment to initiate anticoagulant therapy.

Low molecular weight heparin (LMWH) is the first-line class. Treatment was associated with reduced thrombus progression and a high rate of complete repermeabilization of the portal lumen. Another extremely important aspect of low molecular weight heparin treatment is the decreased risk of variceal bleeding. The mechanism is represented by the reduction of vascular complications of cirrhosis and the reduction of portal hypertension by rapidly stopping the progression of the thrombus and portal repermeabilization. A meta-analysis comprising 4 studies that include 158 patients mentions a bleeding rate of 2% in anticoagulated patients versus 12% for those without LMWH therapy[9]. Furthermore, 6 studies including 257 patients showed the same 11% rate of major and minor bleeding events, both for patients with as well as for those without anticoagulant treatment[9].

Unfractionated heparin has been studied with slightly less interest. Its use is essential but limited to patients with renal impairment[6].

Vitamin K antagonists can be used successfully, the target INR being in the range of 2-3. They are equally effective in arresting thrombus progression, with the same rates of portal reperfusion, but a lower percentage of total reperfusion compared



with using LMWH[8]. The relatively narrow therapeutic range and the need for regular monitoring of the INR, the hepatic metabolism of the drug and the variability of INR accuracy in patients with impaired liver function are factors that may make effective therapy difficult in some cases[4].

Direct oral anticoagulants (DOACs) have limited indications in patients with chronic hepatopathies. To determine whether they can be administered to a cirrhotic, the Child-Pugh score must be calculated: DOACs can be used in those with Child-Pugh class A. They have to be administered with caution and dose adjustment in those with Child-Pugh B and have to be avoided in patients with class C cirrhosis[4].

The initially recommended duration of anticoagulant therapy is 6 months, in the absence of other procoagulant conditions, with periodic reassessment of bleeding risk and ultrasound monitoring of portal postthrombotic status[9]. Ultrasound reevaluation 3 months after discontinuation of anticoagulant therapy is recommended[3].

Patient prognosis

The causality relationship between recent portal vein thrombosis and portal hypertension has not been established yet. As well as the order of occurrence of the specific complications and liver disease progression and the in this clinical context, it remains to be determined if thrombosis occurs as a complication of progressively worsening portal hypertension or if it occurs independently as an event responsible for worsening the disease and increasing the mortality.

For patients awaiting liver transplantation, portal vein patency is an important prognostic factor: portal vein occlusion at the time of transplantation is associated with poor post-transplant survival rates.

The natural evolution of cases of recent portal vein thrombosis is also highly variable. Spontaneous repermeabilization has been observed in up to 40% of cases, usually within the first 3 months[2], while other cases may progress to chronicity and portal cavernoma formation.

Conclusion

Summarizing the recommendations of current international guidelines and the conclusions of recent meta-analyses, it is considered reasonable to initiate anticoagulant therapy in most, but not all patients with recent portal vein thrombosis in the context of liver cirrhosis and in the absence of contraindications.

The anticoagulant class of choice is low molecular weight heparins, given their safety and efficacy profile in these patients. The

disadvantages of this class are the lack of paraclinical monitoring markers for the efficiency of anticoagulation and the reduced subcutaneous absorption in patients with severe edema and ascites.

Anticoumarins may represent a strong alternative, but the INR lability in some patients with cirrhosis and the delicate balance of coagulation factors in these patients may create difficulties in initiating or maintaining treatment[9].

An expectative attitude of monitoring thrombus evolution and clinical status without initiation of anticoagulant therapy is the ideal option for a fraction of patients: those with partial, asymptomatic portal vein occlusion and without thrombosis of portal tributaries as well as for those with increased hemorrhagic risk or uncontrolled active bleeding[9].

The lack of randomized clinical trials, firm guidelines and standardized therapeutic algorithms poses serious challenges in deciding anticoagulation and choosing the optimal drug class for patients with recent portal vein thrombosis and cirrhosis. In this context, the decision should be made taking into account the entire clinical-biological status of the patient: Child-Pugh class, liver and kidney function, platelet count and coagulogram.

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