

Initial management of noncirrhotic splanchnic vein thrombosis: When is anticoagulation enough?

Pranavi Ravichandran MD¹, Kris P Croome MD MS^{1,2}, Michael J Kovacs MD FRCPC³,
Alejandro Lazo-Langner MD MSc^{3,4}, Roberto Hernandez-Alejandro MD^{1,2}

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BACKGROUND: The optimal initial treatment of splanchnic vein thrombosis is uncertain. Anticoagulant therapy has been shown to be associated with vessel recanalization and decreased recurrence. Furthermore, information regarding potential predictors of chronic complications is not well understood.

METHODS: A retrospective cohort study involving consecutive patients diagnosed with first-episode noncirrhotic splanchnic vein thrombosis referred to the thrombosis clinic of the authors' institution between 2008 and 2011 was conducted. Demographic and clinical information was collected. The response to initial anticoagulant therapy was evaluated by determining radiographic recanalization of vessels and clinical resolution (defined as the absence of ongoing splanchnic vein thrombosis symptoms or complications requiring treatment beyond anticoagulant therapy).

RESULTS: Twenty-two patients were included. Anticoagulant therapy alone resulted in vessel recanalization in 41% of patients and 68% achieved clinical resolution. Two patients experienced bleeding events. Factors associated with a lack of clinical resolution included signs of portal hypertension/liver failure on presentation, complete vessel occlusion at diagnosis, presence of a myeloproliferative disorder or *JAK2*^{V617F} tyrosine kinase mutation and the absence of a local/transient predisposing factor.

CONCLUSIONS: Anticoagulant therapy appeared to be an effective initial treatment in patients with splanchnic vein thrombosis. Clinical factors may help to identify patients who are at risk for developing complications thus requiring closer monitoring. These findings were limited by the small sample size and need to be explored in larger prospective studies.

Key Words: Anticoagulation; Portal hypertension; Splanchnic vein thrombosis; Therapy

Splanchnic vein thrombosis unrelated to primary liver disease is a rare and poorly understood clinical phenomenon; information pertaining to its optimal management is limited (1-4). Anticoagulant therapy in patients with splanchnic vein thrombosis has been shown to be effective in recanalizing thrombosed vessels and alleviating symptoms (2). For chronic splanchnic vein thrombosis with ongoing risk factors, prolonged or indefinite anticoagulant therapy has been credited with decreasing recurrence rates and preventing symptom progression (4,5).

When medical management is not effective, progressive or recurrent splanchnic vein thrombosis can cause mesenteric ischemia or portal hypertension requiring surgical or endoscopic management. Given its reported safety and efficacy, most clinicians begin

La prise en charge initiale de la thrombose veineuse splanchnique non cirrhotique : quand l'anticoagulation suffit-elle?

HISTORIQUE : On ne connaît pas le traitement initial optimal de la thrombose veineuse splanchnique. L'anticoagulothérapie s'associe à une recanalisation des vaisseaux et à une diminution des récurrences. De plus, on comprend mal les données sur les prédicteurs potentiels des complications chroniques.

MÉTHODOLOGIE : Les auteurs ont mené une étude rétrospective de cohorte auprès de patients consécutifs ayant un diagnostic de premier épisode de thrombose veineuse splanchnique aiguë vers la clinique de thrombose de leur établissement entre 2008 et 2011. Ils ont colligé des renseignements démographiques et cliniques. Ils ont évalué la réponse à l'anticoagulothérapie initiale en déterminant la recanalisation radiographique des vaisseaux et leur résolution clinique (définie comme l'absence de symptômes continus de thrombose veineuse splanchnique ou de complications exigeant un traitement en plus de l'anticoagulothérapie).

RÉSULTATS : Vingt-deux patients ont participé à l'étude. L'anticoagulothérapie seule a assuré la recanalisation des artères chez 41 % des patients, dont 68 % ont profité d'une résolution clinique. Deux patients ont souffert d'hémorragies. Les facteurs associés à l'absence de résolution clinique incluaient les signes d'hypertension portale ou d'insuffisance hépatique à la présentation, une occlusion complète des vaisseaux au diagnostic, la présence d'un trouble myéloprolifératif ou de la mutation de la tyrosine kinase *JAK2*^{V617F} et l'absence de facteur prédisposant local ou transitoire.

CONCLUSIONS : L'anticoagulothérapie semblait efficace comme traitement initial de la thrombose veineuse splanchnique. Des facteurs cliniques peuvent contribuer à dépister les patients vulnérables aux complications et qui ont donc besoin d'une surveillance plus attentive. Ces observations étaient limitées par la petite taille de l'échantillon et devront être évaluées dans le cadre d'études prospectives plus vastes.

management with anticoagulant therapy alone, resorting to more invasive interventions following an ineffective trial of medical management (2-4,6). In the present study, we aimed to describe our experience with the treatment of splanchnic vein thrombosis and to identify potential predictors of the need for additional interventions beyond anticoagulant therapy.

METHODS

A retrospective cohort study including consecutive adult patients with a newly diagnosed first episode of noncirrhotic splanchnic vein thrombosis referred to the Thrombosis Clinic at the London Health Sciences Centre in London, Ontario, between January 2008 and August 2011 was conducted. Information regarding demographic and clinical

¹Department of Surgery, Division of General Surgery, University of Western Ontario; ²Multi-Organ Transplant Program, London Health Sciences Centre;

³Department of Medicine, Division of Hematology; ⁴Department of Epidemiology and Biostatistics, University of Western Ontario, London, Ontario

Correspondence: Dr Alejandro Lazo-Langner, Division of Hematology, Department of Medicine, University of Western Ontario, 800 Commissioners Road East, Room E6-216A, London, Ontario N6A 5W9. Telephone 519-685-8500 ext 58833, fax 519-685-8477, e-mail alejandro.lazolangner@lhsc.on.ca

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TABLE 1
Splanchnic vein involvement and degree of occlusion at maximally occlusive site (n=22)

Vessel(s) involved	Degree of occlusion, n			Total, n (%)
	Complete	Partial	Not specified	
Isolated splanchnic vein thrombosis				
Portal vein	2	2	2	6 (27.3)
SMV		5	1	6 (27.3)
Multivessel disease				
Portal vein + SMV + SV	2		3	5 (22.7)
Portal vein + SV	1			1 (4.5)
Portal vein + SMV	1			1 (4.5)
Portal vein + SMV + DVT	1			1 (4.5)
Portal vein + DVT	1			1 (4.5)
Portal vein + BCS	1			1 (4.5)

BCS Budd-Chiari syndrome with hepatic vein thrombosis; DVT Left deep vein thrombosis; SMV Superior mesenteric vein; SV Splenic vein

variables, predisposing factors and thrombophilia was collected. The index date was the date an objectively confirmed diagnosis of portal, splenic and/or superior mesenteric veins was made. Thrombophilia screening was performed in all patients and included prothrombin gene G20210A variant, Factor V Leiden, protein C deficiency, protein S deficiency, antithrombin deficiency, anticardiolipin antibodies, lupus anticoagulant and paroxysmal nocturnal hemoglobinuria. The duration of anticoagulation therapy was also recorded. Patients were classified as having a myeloproliferative disorder if they carried the JAK2^{V617F} tyrosine kinase mutation (7) or if they met current diagnostic criteria for overt myeloproliferative disorder in the absence of the JAK2^{V617F} mutation (8).

The response to initial anticoagulant therapy was assessed by determining radiographic recanalization of vessels on follow-up imaging and clinical resolution. The latter was defined as the absence of ongoing splanchnic vein thrombosis symptoms or complications requiring treatment beyond anticoagulant therapy. Also assessed were the occurrence of major bleeding events according to the definition from the International Society on Thrombosis and Haemostasis (9) as well as clinically relevant nonmajor bleeding. Groups were compared using the Mann-Whitney or Fisher's exact tests, as appropriate; $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

Between January 2008 and August 2011, 22 patients (nine female; mean age 51 years [range 29 to 67 years]) who received anticoagulant therapy and did not demonstrate primary cirrhotic disease were referred to the authors' clinic and included in the study. Table 1 summarizes the distribution of vessels involved. Comorbid conditions included history of deep vein thrombosis or pulmonary embolism (n=5), hypertension (n=4), type 2 diabetes (n=1), obesity (n=1), inflammatory bowel disease (n=2), recent or ongoing nonhepatic malignancy (n=5), and recent abdominal surgery (n=6). A local or transient risk factor for splanchnic vein thrombosis formation was identified in 50% of the patients. Among the remaining patients, eight had thrombophilic disorders identified (Table 2). Myeloproliferative disorders were identified in six patients (27.3%). No underlying risk factors for splanchnic vein thrombosis were identified in three patients.

Four patients were diagnosed incidentally on staging computed tomography scans for colorectal cancer or lymphoma. Another patient was initially imaged due to recurrent, transiently elevated liver enzyme levels. All symptomatic patients were diagnosed with splanchnic vein thrombosis within 24 h to three weeks from the onset of symptoms.

TABLE 2
Risk factors for splanchnic vein thrombosis (n=22)

Factor	n (%)
Local/transient etiology	11 (50)
Malignancy*	5 (22.7)
Recent abdominal surgery*	7 (31.8)
Idiopathic small bowel obstructions	1 (4.5)
Diverticulitis	1 (4.5)
Chronic pancreatitis with recent stenting	1 (4.5)
Systemic thrombophilia	8 (36.4)
Myeloproliferative disorder/JAK2V617F tyrosine kinase mutation†	6 (27.3)
Prothrombin gene G20210A variant	2 (9.1)
Factor V Leiden	4 (18.2)
Multiple thrombophilia	4 (18.2)
Unknown	3 (13.6)

*In three patients, abdominal surgery was due to malignancy; †In one patient, myeloproliferative disorder was biopsy proven but JAK2 negative

The most common presenting symptom was abdominal pain (54.5%). Other presenting complaints included abdominal distension and decreased bowel movements, marked hepatosplenomegaly secondary to myelofibrosis and fever in a patient with a history of recurrent diverticulitis. Of note, one patient presented with upper and lower gastrointestinal bleeding and an acute surgical abdomen secondary to intestinal ischemia. Four patients had documented signs of portal hypertension or hepatic dysfunction at the time of diagnosis of splanchnic vein thrombosis. These included nonbleeding gastroesophageal varices (n=2), hepatosplenomegaly (n=3), ascites (n=2) and jaundice (n=2). Screening endoscopy was not routinely offered to all patients included in the present review, and information pertaining to the presence or absence of gastroesophageal varices was only available for these four patients.

All patients included in the study received anticoagulant therapy promptly after diagnosis. Treatment consisted of unfractionated heparin or low molecular weight heparin followed by oral vitamin K antagonists. Patients who recurred were switched to long-term treatment with low molecular weight heparin at the discretion of the treating physician who also determined the duration of anticoagulant therapy. All of the 11 patients with only clear local or transient risk factors completed a short course of anticoagulant therapy (six months in 10 patients and three months in a patient whose course was stopped early in anticipation of an unrelated surgical procedure). All remaining patients were prescribed indefinite anticoagulation.

No patients underwent thrombolytic therapy. In one patient who was diagnosed with mesenteric vein thrombosis intraoperatively, visible thrombi were manually removed during laparotomy and anticoagulant therapy was started postoperatively. The mean follow-up period for all patients was 22 months.

Treatment outcomes and predictors

Follow-up imaging was available for 21 patients because one patient died during follow-up from concurrent metastatic colorectal cancer. Vessel recanalization was documented in nine patients (41%) and clinical resolution was achieved in 15 (68%). Of the 11 patients who received short-course anticoagulation for splanchnic vein thrombosis associated with only local or transient risk factors, eight (73%) obtained vessel recanalization and 10 (91%) resolved clinically. The local/transient risk factor group had an increased association with recanalization ($P=0.008$) and tended to achieve clinical resolution more frequently ($P=0.063$) than individuals with identified thrombophilias or unknown etiologies. The clinical complications and subsequent interventions made in patients who did not achieve clinical resolution are described in Table 3.

TABLE 3
Complications and subsequent interventions in patients failing to achieve clinical resolution

Patient	Thrombosed vessels	Clinical complications	Interventions
1	Portal vein	Deceased (ongoing malignancy)	
2	Portal vein	Development of new nonbleeding varices	Beta-blockers
3	Portal vein	Persistence of nonbleeding varices	Beta-blockers
	Superior mesenteric vein	Massive splenomegaly + compressive gastric outlet obstruction	Splenectomy
	Splenic vein		
4	Portal vein	Transient rethrombosis and abdominal pain	
	Splenic vein		
5	Portal vein	Portocaval shunt occlusion	Urgent liver transplant
	Hepatic veins (Budd-Chiari syndrome)	Liver failure	
	Portocaval shunt		
6	Portal vein	Enlargement of nonbleeding varices	Discontinuation of anticoagulant therapy
	Deep vein thrombosis (leg)	Rethrombosis (deep vein thrombosis)	Beta-blockers Resume anticoagulant therapy
		Variceal hemorrhage	Splenectomy Devascularization of gastroesophageal junction Discontinuation of anticoagulant therapy Variceal band ligation
		Rethrombosis: Portal vein	Restart indefinite anticoagulant therapy
		New thrombosis: Inferior vena cava and left renal vein	
7	Mesenteric veins (diagnosed intraoperatively)	Acute ischemic gut at initial presentation	Manual thrombectomy Small bowel resection

Factors associated with a lack of clinical resolution (and subsequent need for further interventions) included signs of portal hypertension/liver failure on presentation ($P=0.005$), complete vessel occlusion at diagnosis ($P=0.029$), presence of a myeloproliferative disorder or $JAK2^{V617F}$ tyrosine kinase mutation ($P=0.004$) and the absence of a local/transient predisposing factor ($P=0.034$). There did not appear to be any statistically significant association between outcome and age, sex or clinical presentation. Of the four patients with incidental diagnoses in the context of active or treated malignancy, three attained persistent radiographic recanalization and one died from concurrent metastatic colonic malignancy.

There was one event each of major and clinically relevant nonmajor bleeding. One patient experienced recurrent lower gastrointestinal bleeding that ceased on completion of a six-month course of anticoagulant therapy, and variceal hemorrhage occurred in one patient who subsequently underwent endoscopic variceal band ligation followed by resumption of prolonged anticoagulant therapy for recurrent splanchnic vein thrombosis.

DISCUSSION

In the present study, we report our experience with the treatment of patients with noncirrhotic splanchnic vein thrombosis using anticoagulant therapy. We found that approximately one-half of the patients achieved recanalization of the involved vessels, particularly among patients with a transient or local risk factor. Other studies have also reported partial or complete recanalization in 33% to 90% of cases with anticoagulant therapy alone (1,2,4,10). However, in addition to vessel recanalization, the presence of clinical resolution (and avoidance of additional therapies) is also a clinically relevant parameter that has not been frequently studied. In fact, studies investigating lower-extremity deep vein thrombosis have not demonstrated that radiographic resolution alone is associated with improved rates of symptom-free survival or recurrence (11). In this regard, we found that clinical resolution occurred more frequently in patients with transient/local risk factors, in those with partial vein occlusions, in those without signs of portal hypertension or liver failure, and in those without the $JAK2^{V617F}$ mutation. This information may help to identify patients at higher risk for developing chronic complications and, thus, requiring closer monitoring. There did not appear to be any

statistically significant association between outcome and age, sex or clinical presentation in the current study.

In patients with ongoing prothrombotic disorders, prolonged anticoagulant therapy has been found to decrease the rate of recurrent thrombotic complications by >60% (4,5). While there are no trial data available to identify specific patient groups in which prolonged anticoagulant therapy is necessary to prevent splanchnic vein thrombosis complications, some authors suggest prescribing long-term anticoagulant therapy for all patients with thrombophilic disorders and any patient who presents with mesenteric vein thrombosis due to the risk of recurrent bowel ischemia (1,3,5).

However, the use of anticoagulant therapy has been associated with an increased risk for bleeding, particularly in the presence of additional risk factors. Therefore, the risk of using anticoagulant therapy should be carefully considered in each patient. Based on a retrospective cohort study involving 136 patients, Condat et al (5) reported no significant association between anticoagulant therapy and the risk or severity of variceal bleeding in splanchnic vein thrombosis patients. They published a risk-benefit ratio that favoured the use of anticoagulant therapy to prevent thrombus progression, thereby preventing further increases in portal pressure (5). In contrast, some authors have advised against the use of long-term anticoagulant therapy in light of significant variceal hemorrhage rates; however, these recommendations were based on study populations that included patients with cirrhotic splanchnic vein thrombosis (12). The natural history of variceal bleeding in primary splanchnic vein thrombosis patients appears to differ from that of cirrhotic patients, with decreased severity when matched for similar variceal characteristics, decreased frequency of bleeds and overall better outcomes (3,6). This may be due to an intact coagulation pathway in the context of normal liver function (3). Even in cirrhotic patients, however, anticoagulation may be beneficial. In a recent randomized trial involving 70 advanced cirrhotic patients, Villa et al (13) demonstrated that prophylactic low molecular weight heparin was both safe and effective in preventing the development of portal vein thrombosis. They cited improved survival in the anticoagulation group, less hepatic decompensation and no bleeding complications.

In cirrhotic and noncirrhotic patients, variceal size, endoscopic features and a history of previous bleeds can help to predict future

bleeding risk and may guide the decision to proceed with endoscopic treatment before anticoagulant therapy or to institute a thorough endoscopic screening protocol. It may be advisable to screen all patients with portal venous thrombosis endoscopically (14). Alternatively, one could restrict endoscopic assessment to patients with ultrasonographic features suggestive of esophageal varices (15). While some have proposed that the presence of nonbleeding varices may be an indication to hold or shorten anticoagulation courses (12), this does not optimally minimize morbidity and mortality due to the poor outcomes of progressive splanchnic vein thrombosis. Recanalization is the best treatment for varices formed secondary to splanchnic thrombosis and, as such, withholding anticoagulation should probably be discouraged in the absence of high bleeding risk (16). Beta blockade remains an effective means of preventing variceal bleeding in general (3), although variceal band ligation may be preferable in the setting of portal vein thrombosis (14) and is effective 90% of the time in hemorrhage prevention (16). A dual approach of endoscopic and medical management has led to more pronounced variceal regression (14). Therefore, a pragmatic approach may involve prophylactic endoscopic variceal band ligation with concurrent anticoagulant therapy (3). In the setting of variceal hemorrhage, endoscopic eradication significantly reduces the risk of recurrent bleeding in these patients, allowing for ongoing anticoagulation for treatment of their underlying thrombotic pathology (3).

Taking the previous information into consideration, it is our practice to consider anticoagulation for all patients with newly diagnosed splanchnic vein thrombosis if there is no contraindication, particularly esophageal varices with endoscopic high-risk bleeding features. For patients with events associated with transient risk factors, we consider three to six months of anticoagulation. For patients without associated risk factors and in the presence of high-risk thrombophilias (eg, combined defects, antiphospholipid antibodies, myeloproliferative neoplasms), we consider indefinite anticoagulation. However, periodic reassessments are performed to re-evaluate bleeding risk and thrombus resolution. In patients without evidence of improvement during follow-up (eg, thrombus persistence with development of collaterals and/or cavernomatous transformation), we consider discontinuation of anticoagulants due to futility.

Given the efficacy and safety of anticoagulant therapy and the overall low mortality rate associated with splanchnic vein thrombosis, the general consensus is to reserve invasive procedures such as transjugular intrahepatic portosystemic shunt procedures for cases in which anticoagulant therapy and endoscopy are ineffective (2,3,6,10). Additionally, several surgical techniques have been used in this patient population, including splanchnic-intrahepatic portal bypass, splenectomy and devascularization of the gastroesophageal junction, which has reportedly been more effective in spontaneous splanchnic vein thrombosis than in cirrhotic patients (3). Given the heterogeneity of splanchnic vein thrombosis, its complications and its predisposing factors, the choice of interventions is difficult to standardize and is best informed by patient factors.

In addition to splanchnic vein thrombosis itself, concomitant diseases – particularly cancer and myeloproliferative disorders – are an important cause of morbidity and mortality in these patients (3,4,6). The relatively recent description of the association between splanchnic vein thrombosis and the presence of the *JAK2*^{V617F} tyrosine kinase mutation found in myeloproliferative disorders should prompt its investigation in all patients because these disorders require further hematological work-up (7,17,18). In addition, some authors suggest screening for thrombophilic disorders in splanchnic vein thrombosis patients regardless of apparent local etiology because both local and thrombophilic factors are believed to interact in the pathogenesis of splanchnic vein thrombosis (4,19). It is our practice to investigate patients with idiopathic noncirrhotic splanchnic vein thrombosis for thrombophilia, although the clinical value of this practice is yet to be determined. Finally, the role of screening for other potential thrombotic conditions, such as paroxysmal nocturnal hemoglobinuria, is at

present unclear, particularly given its rarity, although patients with this condition have been reported to frequently develop splanchnic vein thrombosis (20).

The limitations of the present study were those inherent in its single-centre retrospective design, as well as the observational approach required to analyze a rare, heterogenous and potentially life-threatening condition. Another limitation was that six of our patients had the diagnosis made incidentally on computed tomography scan. The significance of an incidental finding of splanchnic vein thrombosis is not certain. Finally, other limitations include the small study population and nonstandardized treatment and screening algorithms. In the absence of randomized controlled trials, observational studies may help to inform treatment practices; however, our findings should certainly be regarded as hypothesis generating.

CONCLUSION

Based on our experience and that of others, the use of initial anticoagulant therapy appears to be a reasonable option in the initial management of patients with splanchnic vein thrombosis in the absence of contraindications to anticoagulation. The presence of certain clinical factors may help to identify patients at higher risk for developing chronic complications and need for further therapy, thus requiring closer monitoring. These findings need to be further explored in larger prospective studies to provide robust clinical recommendations.

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