Original Article

The use of nonselective beta blockers is a risk factor for portal vein thrombosis in cirrhotic patients

Rosa Zampino, Rita Lebano, Nicola Coppola[1], Margherita Macera[1], Anna Grandone[2], Luca Rinaldi, Ilario De Sio[3], Antonella Tufano[4], Gianfranca Stornaiuolo[1], Luigi E Adinolfi, Emanuele Durante-Mangoni[3], Gaeta G Battista[1], Alferio Niglio[3]

Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, Infectious Diseases, [1]Department of Public Medicine, [2]Department of Pediatrics, [3]Department of Clinical and Experimental Medicine and Surgery, University of Campania "Luigi Vanvitelli", [4]Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

Abstract

Background/Aim: A reduction in portal vein inflow velocity seems to predispose to the emergence of portal vein thrombosis (PVT). Nonselective β-blockers (NSBBs), used to prevent variceal bleeding, may increase the development of PVT by reducing portal vein inflow velocity. In this retrospective case-control study, we evaluated the risk factors and clinical features of a first event of PVT in 130 cirrhotics, 19 (15%) with (PVT group) and 111 (85%) without PVT (non-PVT group).

Patients and Methods: Patient evaluation and NNBB treatment were carried out according to the AASLD guidelines.

Results: PVT was prevalently partial (84%) and asymptomatic (84%). Patients with PVT were treated with different regimens, and resolution of thrombosis was observed in about 50% of the cases. In both groups, HCV was the most frequent cause of cirrhosis and Child–Pugh score A was prevalent. Ascites and esophageal varices were more frequent in the PVT group ($P = 0.05$ and <0.000, respectively). Treatment with NSBBs was significantly more frequent in the PVT group than in the non-PVT group ($P < 0.000$). PVT was associated with higher prevalence of chronic renal disease ($P = 0.002$), higher PT impairment ($P = 0.003$) and lower AST and ALT ($P = 0.000$). At multivariate logistic regression analysis, history of esophageal varices ($P = 0.007$) and NSBB treatment ($P = 0.0003$) were independent risk factors significantly associated with PVT.

Conclusions: Esophageal varices and NSBB treatment were independent risk factors of PVT. Larger studies should evaluate the risk between variceal bleeding and portal vein thrombosis of using NSBBs, particularly in the prevention of first bleeding in nonadvanced liver cirrhosis.

Keywords: Cirrhosis, nonselective beta blockers, portal vein thrombosis

Address for correspondence: Dr. Rosa Zampino, Department of Medical, Surgical, Neurological, Metabolic and Aging Sciences, University of Campania "Luigi Vanvitelli", Unit of Infectious and Transplant Medicine A.O.R.N. dei Colli - Ospedale Monaldi, Via Ettore Ruggieri, Naples, Italy.
E-mail: rosa.zampino@unicampania.it

INTRODUCTION

Portal vein thrombosis (PVT), an obstruction of the portal vein or its branches, is common in patients with cirrhosis; in prospective and retrospective studies, PVT ranges between 8% and 20% in relation to different parameters such as the time of observation,

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the population studied, and the diagnostic methods used.[1-6]

PVT is also related to the stage of liver disease, less frequent in compensated cirrhosis (about 1%) than in decompensated cirrhosis or in patients awaiting liver transplant (up to 40%).[6-9] PVT is a risk factor of death in patients with cirrhosis.[10,11] It has been demonstrated that a reduction in portal vein inflow velocity predisposes to the emergence of PVT,[12-14] whereas portal venous congestion leads to vascular dysfunction with a vasoconstrictor pathway disorder.[15] These vascular alterations, together with an unstable balance in coagulation, typical mainly of advanced chronic liver disease,[16,17] constitute the pathological bases of PVT in cirrhosis.

As esophageal variceal bleeding is also an important risk factor of death in cirrhotic patients,[18,19] nonselective β-blockers (NSBBs) are currently used in the prevention of this serious event[18,19] in high-risk patients. Because a reduction in portal vein inflow velocity may favor the development of PVT,[12,13] it has been hypothesized that, by reducing portal vein inflow velocity, NSBBs could potentially increase the development of PVT.[20] In contrast, a more recent study that analyzed variables associated with PVT in a large Italian cirrhotic population did not find any difference regarding NSBB treatment between patients with or without PVT.[6]

We retrospectively evaluated the risk factors and clinical features associated with the first event of PVT in consecutive cirrhotic patients observed in the last 5 years.

PATIENTS AND METHODS

We retrospectively analyzed the data of cirrhotic patients with a first event of PVT observed at the Internal Medicine, Infectious Diseases and Gastroenterology Units of the University of Campania "Luigi Vanvitelli" from 2011 to 2015. Considering that the incidence of PVT in cirrhosis ranges 8–20% of cases, we evaluated for comparison patients with cirrhosis without PVT matched for Child–Pugh score at the same units in the first 6 months of 2011. The diagnosis of cirrhosis was made on histological or clinical/ultrasonographic (US) examination and all patients were followed in accordance with good clinical practices. Clinical evaluation, liver function tests, US scan follow-up, esophagogastroduodenoscopy (EGD) follow-up, and NSBB treatment (propanolol) were prescribed according to the AASLD guidelines.[18,21] Propanolol was administered at a dose of 20 mg bid, and reduced when heart rate was under 56/min. Anthropometric parameters, risk factors, clinical stage, and liver and renal function tests were evaluated in both groups; in patients with PVT, the data at the time of development of PVT were evaluated, whereas in patients without PVT the latest available data were considered. Furthermore, in the group with PVT, the extent of thrombosis, clinical presentation at diagnosis, treatment, and outcome were also evaluated.

Patients with PVT had been treated with different therapy regimens and had been followed-up throughout treatment and after discontinuation for at least 3 months.

The study was approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli."

Definition of PVT

In accordance with the literature recommendations,[22,23] PVT was defined as the presence of a complete or partial obstruction of the main branch or afferent branches detected by ultrasound examination. The venous thrombus appeared as echogenic material in the vessel lumen with consequent partial or total failure of the blood flow detected by color or power Doppler. Presence of PVT is routinely evaluated in cirrhotic patients during examination. US evaluation was performed by a single operator with high experience in the field (>1000 exams) working for all the units involved in the study.

Statistical analysis

Continuous variables were expressed as mean and standard deviation and categorical variables as absolute and relative frequencies. Differences in the mean values were evaluated by an unpaired Student's *t*-test for normal distribution, the Mann–Whitney test for nonparametric data, and Chi-square test was applied to categorical variables.

A P value <0.05 was considered to be statistically significant. A logistic regression was performed to calculate the odds of showing PVT using all parameters significantly correlated to it at univariate analysis. Statistical analysis was performed using StatGraph, version 3.0 software for Windows (Statgraphics Technologies, Inc., The Plains, Virginia, USA).

RESULTS

Clinical presentation of PVT, treatment, and outcome.

Nineteen cirrhotic patients presented a first event of PVT during the observation period. It was prevalently partial (84%), asymptomatic (84%), and diagnosed by US scan (100%), often during scheduled follow-up [Table 1].

In accordance with the current guidelines, all patients received anticoagulant therapy for at least 3 months after

Table 1: Clinical presentation, diagnosis, treatment and outcome of PVT

Extent of occlusion	
Partial	16 (84%)
Complete	3 (16%)
Clinical presentation at time of diagnosis	
Yes	3 (16%)
Abdominal Pain	1 (6%)
Ascites	2 (10%)
No	16 (84%)
Modality of diagnosis	
Ultrasound	19 (100%)
Computed tomography/magnetic resonance imaging	0 (0%)
Type of anticoagulant therapy	
Low-molecular weight heparin (LMWH)	17 (89%)
Vitamin K antagonist (VKA)	2 (11%)
Duration of anticoagulant therapy (days)	
Cirrhotics median (range)	120 (7-365)
Recanalization	11 (58%)
Relapse after recanalization	5 (26%)
Persistence of thrombosis	8 (42%)
Adverse events	
New thrombosis	0 (0%)
All-causes mortality	0 (0%)
Decompensated cirrhosis	6 (31%)

TIPS: Transjugular intrahepatic portosystemic shunt; OLT: Orthotopic liver transplantation, Data presented as n (%)

the diagnosis of thrombosis. Most patients (89%) were treated with low-molecular weight heparin (100 IU/kg every 12 hours) and 2 (11%) with vitamin K antagonist (VKA, warfarin) following the International Normalized Ratio (INR).

A resolution of thrombosis was observed in about 50% of the patients, but 15% of those who had been treated with LMWH relapsed [Table 1].

During treatment, no patient experienced major bleeding while 6 patients (31%) experienced an episode of ascites. There was no death from any cause or no new thrombotic events during treatment.

PVT risk factor analysis

The data of 130 cirrhotic patients, 19 (15%) with PVT and 111 (85%) controls, were retrospectively collected. Their general characteristics according to the presence or absence of PVT are shown in Table 2.

Patients were in equilibrium concerning age and gender distribution. In both groups, HCV was the most frequent cause of cirrhosis, and Child–Pugh score A was prevalent. The comorbidities most frequently observed were essential hypertension and diabetes mellitus; about 20% of patients in both groups were smokers. Only 1 patient with PVT had a history of HCC which was cured before the emergence of PVT.

Table 2: General characteristics of cirrhotic patients with or without PVT

	PVT	NO PVT	*P*
N. of patients	19	111	
Males	8 (42)	56 (50)	0.83
Age	62±11.20	64±9.96	0.35
BMI	25±3.89	27±4.40	0.1
Diabetes mellitus	4 (21)	18 (16)	0.14
Hypertension	11 (58)	12 (11)	0.002
Smoker	4 (21)	20 (18)	0.66
Current therapies			
Non-selective β-blockers	18 (95)	10 (9)	0.000
Etiology			
HBV	4 (21)	4 (3)	0.034
HBV + HDV	2 (11)	0	0.02
HCV	7 (36)	88 (79)	0.000
Alcohol	1 (5)	5 (4)	0.88
Cryptogenic	2 (11)	0	0.02
NASH	0	2 (2)	0.78
Primary biliary cholangitis	1 (5)	2 (2)	0.35
Multifactorial	2 (11)	10 (9)	0.832
Child-pugh score			
A	13 (68)	88 (79)	0.05
B	6 (31)	15 (13)	
C	0	8 (7)	
History of ascites	8 (42)	13 (11)	0.05
History of PSE	2 (10)	6 (5)	0.60
History of EV	18 (95)	33 (30)	0.000
History of HCC	1 (5)	3 (2)	0.71

PVT: Portal Vein Thrombosis, PSE: Porto systemic encephalopathy, EV: Esophageal varices, HCC: Hepatocellular carcinoma, OLT: Orthotopic liver transplantation, Data presented as mean ± standard deviation, or n (%) as appropriate

Signs of portal hypertension, such as history of ascites and esophageal varices, were more frequent in the PVT group than in the non-PVT group ($P = 0.05$ and <0.000, respectively).

Treatment with NSBBs was significantly more frequent in patients with PVT than in those without PVT ($P < 0.000$). Duration of NSBB treatment had not been clearly recorded for all patients, particularly for those who had started treatment before being followed-up at one of the centers involved in the present study. NSBB treatment was continued after PVT for all patients.

Liver function tests were within the normal value in the majority of patients and were similar in both groups [Table 3]. Patients with PVT had a higher prevalence of chronic renal disease ($P = 0.002$), higher PT impairment ($P = 0.003$) and lower AST and ALT levels ($P = 0.000$).

At multivariate logistic regression analysis only history of esophageal varices ($P = 0.007$) and NSBB treatment ($P = 0.0003$) were independent risk factors significantly associated with PVT [Table 4].

DISCUSSION

We found a high presence of PVT (15%) in the population studied; a history of ascites and esophageal varices were more frequent in patients with PVT than in those without PVT. In contrast with the literature data,[6-9] no patient with PVT had Child–Pugh score C but a high percentage of PVT (71%) was observed in Child–Pugh score A patients. HCC did not seem to influence PVT development.

Most of our patients with PVT showed esophageal varices and were treated with NSBBs. Few data are available on NSBB treatment and PVT development. Qi and colleagues hypothesized that NSBBs, generally used for the prevention of variceal bleeding in cirrhotic patients, might favor PVT by decreasing portal vein inflow velocity.[5] To the best of our knowledge only one report by Pellicelli *et al.*, stated that the use of NSBBs in cirrhosis was an independent risk factor for the development of PVT,[13] however, the patients' Child–Pugh scores were not specified in this study. Our data are in perfect concert with those of Pellicelli *et al.*, but both studies have a low number of patients. In a recent study on a large Italian cirrhotic population, Violi *et al.* did not find any difference in the use of NSBBs between patients with or without PVT.[6] This was a cross-sectional study and did not focus on the emergence of a first episode of PVT as did our study and that of Pellicelli *et al.* However, Violi *et al.* found that previous PVT, upper gastrointestinal bleeding, Child–Pugh Class B/C, HCC, and old age were independently associated with PVT.[6]

Table 3: General liver and renal function tests in patients with or without PVT

	PVT	NON- PVT	*P*
AST U/L	35±26	77±57	0.000
ALT U/L	31±26	79±71	0.000
Bil T mg/dl	1.1±0.7	1.2±1	0.4
ALP U/L	102±49	140±86	0.09
PCHE U/L	5350±1872	4925±2661	0.9
Hb g/dl	12±1.4	12.9±1.9	0.06
WBC/mm^3	4350±2468	4857±1991	0.3
PLT/mm^3	92355±88149	120145±68129	0.07
PT %	65.4% ±12.52	78.48% ±17.60	0.003
Crea mg/dl	0.8±0.2	0.8±0.3	0.5
Urea mg/dl	43±17.55	41±19.92	0.8
Glucose mg/dl	84.5±18.4	115±29	0.001
Albumin mg/dl	3.6±0.5	3.7±0.6	0.2
GFR			
Normal	14 (73)	105 (94)	0.002
Mild chronic renal impairment	5 (27)	6 (6)	0.002

PVT: Portal Vein Thrombosis; ALT: Alanine Transferase; AST: Aspartate Transaminase; Bil T: Total bilirubin; ALP: Alkaline phosphatase; PCHE: Pseudocholinesterase; Hb: Hemoglobin; WBC: white blood cells; PLT: Platelets; PT %: Prothrombin time; Crea: Serum creatinine; GFR: Glomerular filtration rate measured by modification of diet in renal disease (MDRD) formula, Data presented as mean ± standard deviation, or n (%) as appropriate

Our study population consisted, for more than 70%, of patients with Child–Pugh score A and signs of portal hypertension (varices and ascites); it can be hypothesized that NSBB treatment particularly enhances the emergence of PVT in patients who have a non-advanced stage of liver disease and portal hypertension, thus creating an additive effect on the decrease of portal flow velocity. At present, we have no further explanation for the development of PVT in this group of patients, but further study could specify this issue.

PVT is a multifactorial manifestation during cirrhosis history and pro-coagulant factors may also be involved; unfortunately, we do not routinely test patients for a complete pattern of coagulation factors and do not have the relative data as the study is retrospective.

Certainly other factors could have influenced PVT development correlated to inflammation, hypercoagulability, venous stasis, and anatomical and genetic abnormalities, as observed in transplanted patients.[24,25]

More than 80% of patients with PVT had been treated with enoxaparin, which had been well tolerated. Previous literature data on the management of PVT in cirrhotics are scanty; the studies involved few patients, of different origins and with different types and stages of liver disease;[5,8] LWMH and VKA seem to be the treatments most frequently used, and in an Italian cohort enoxaparin showed efficacy also in preventing PVT development.[26]

The most important limitations of this study are certainly the small number of patients and the retrospective nature, which do not allow definitive conclusions to be drawn; however, this report supports other clinical observations

Table 4: Logistic Regression Analysis for severe PVT

Independent variables	Coefficient	Standard error	Chi-square	*P*	OR	C.I.
Constant	-36.00	191.78				
Platelets	-0.0000	0.0000	0.96	0.32	0.99	0.99-1.0
Child-Pugh			3.38	0.19		
Esophageal varices			14.07	0.007		
Hypertension	1.48	0.85	3.38	0.06	4.4	-0.2-3.1
Beta-blocker use	2.88	0.92	13.4	0.0003	17.8	1.03-4.7

PVT: Portal Vein Thrombosis; Model R-squared=53.5% *P*=0.00001

and general hypotheses regarding the role of NSBBs in the development of PVT, especially in patients with a non-advanced stage of liver disease.[5,13] The risk between variceal bleeding and portal vein thrombosis of using NSBBs, particularly in the prevention of the first bleeding in non-advanced cirrhosis, needs to be evaluated in large trials.

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Conflicts of interest

There are no conflicts of interest.

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