Section: Gastroenterology

Original Research Article

PREVALENCE OF DEEP VEIN THROMBOSIS IN PATIENTS WITH ADVANCED LIVER CIRRHOSIS: RARE ENTITY IN A TERTIARY CARE CENTRE

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Abstract

Background: Venous thromboembolism (VTE) has traditionally been considered rare in Asia. There is scarce Indian data on time trends of deep vein thrombosis (DVT) in chronic liver disease (CLD) in India. The aim of this study to know the prevalence of DVT among cirrhotic patients and to compare clinical presentation of cirrhotic patients with and without DVT. **Materials and Methods:** This was an observational study of patients with liver cirrhosis who were admitted to gastroenterology department SMS hospital Jaipur, during one-year period. All patients with liver cirrhosis during the study period were included. DVT in CLD was established by duplex Doppler ultrasonography of the lower extremities. Patients with splanchnic thrombosis and portal vein were excluded from this study. Patient with DVT were treated with LMWH and warfarin. **Result:** A total of 300 patients with liver cirrhosis were included in this study; 288(96%) among them were male. Patient's mean age was 58.5 ± 10.5 years, ranging from 20 to 65 years. Alcohol accounted for more than 82 % of patients with liver cirrhosis. DVT was found in 8 out of 300 patients (2.67%) patients. There was no significant laboratory difference in patients with and without DVT (platelet count, aminotransferases, c-glutamyl transpeptidase, alkaline phosphatase, total bilirubin levels, and prothrombin time) except serum albumin concentration. **Conclusion:** The prevalence of DVT in patients with liver cirrhosis was 2.6% in our study. Hypoalbuminemia was the only risk factor for developing DVT found in this study and further studies on the mechanisms and prevention of DVT needed in future.

INTRODUCTION

Venous thromboembolism is considered a rare event in patients with liver cirrhosis with unpredictable course and unclear mechanism. Liver produces all factors involved in the coagulation process except Von Willebrand factor, which is secreted by endothelial cells, their production is impaired in case of liver cirrhosis. This impairment results in an increase in prothrombin time. Thus, individuals with advanced liver disease were previously considered as having a hypocoagulant and prohemorrhagic and supposed to be protected against thrombosis. However, this belief is not correct, as patients with cirrhosis also have a reduction in anticoagulant proteins like antithrombin III, protein S, or C, and an increase of procoagulant factors (such as factor VIII or von Willebrand factor). This results in a new balance of pro- and anticoagulation factors, defined as "rebalanced hemostasis". The hemostatic balance is hard to maintain in hepatic insufficiency, and still there may not be a tendency to hemorrhage or thrombosis. Balance can be disrupted in stressful conditions like infections, encephalopathy. Patients with liver cirrhosis are at risk of bleeding because of the increased INR and thrombocytopenia which is enough to protect these patients from developing thrombotic complications, and hence the concept of

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"auto anticoagulation" came. Over the last few years, there are studies that liver disease may be associated with an increased risk of thrombotic complications as well.[1]

Portal vein thrombosis is seen in 10%-25% of the patients with liver cirrhosis, with increased prevalence in patients with more severe disease.[2-4] Data is also emerging regarding occurrence of non-splanchnic venous thromboembolic events (VTE) in these patients, mostly lower extremity deep vein thrombosis (DVT) and pulmonary embolism (PE).[5,6]

The first study on hyper coagulation in cirrhotic patients reported that approximately 0.5% of all admissions resulted in a new diagnosis of a VTE event, which consisted of 65.5% DVT, 19.5% pulmonary embolism (PE), and 15% both.[7]

It has also been proposed that hypercoagulation state may lead to progression of fibrosis, possibly through activation of hepatic stellate cells or as a result of local ischemic changes secondary to hepatic microthrombi.[8] Understanding of hemostatic pathways in cirrhotic is important not only to predict the bleeding or thrombotic complications but also possibility to change the natural course of disease.[9]

In Indian scenario, sufficient data regarding prevalence of DVT in CLD is not available, till date, there are no prospective randomized trials evaluating the incidence of DVT or PE in the advanced cirrhotic population.

The objectives of this study are to know the prevalence of DVT among cirrhotic patients and to compare clinical pictures of cirrhotic patients with and without DVT.

MATERIALS AND METHODS

Study design and subjects: This was an observational study of patients with liver cirrhosis who were admitted to department of gastroenterology, SMS hospital and medical college from April 2017 to March2018. Patients with liver cirrhosis during the study period were included. Diagnosis of liver cirrhosis was based on the patient's history, clinical manifestations of chronic liver disease, and imaging findings by liver ultrasonography or computed tomography. Patient with DVT were also evaluated for coagulation profile those which were available in our setup including serum prothrombin, serum antithrombin III, protein C and protein S.

Diagnosis of DVT: Patients were assessed for the presence of DVT if they presented with clinical symptoms of DVT (i.e., unilateral/asymmetrical swelling and painful leg). Only those patients with confirmed DVT were screened for blood coagulation profile. Deep vein thrombosis was detected using Duplex Doppler ultrasonography of the venous system of the lower extremity based on the criteria of, no flow signal, direct clot visualization, no spontaneous flow and absence of respiratory phasic changes of the evaluated veins. By valsalva manoeuvre or manual compression valvular competency was assessed. Late changes of DVT were seen as presence of collateral veins and partial recanalization of the diseased veins with wall thickening.

Statistical analyses: The prevalence of DVT in cirrhosis was calculated from the total number of patients during the study period. Differences of clinical pictures and laboratory findings between patients with and without DVT were tested using chi-square test for nominal data and the Student t test for numerical data. P value -0.05 was considered statistically significant. Analyses were performed using statistical software Stata, Version 9.0, for Windows PC (Stata Corporation, Texas, USA).

RESULTS

There were 300 patients admitted to the hospital with liver cirrhosis during the study period;288 (96%) among them were male and 12 were female (4%) [Table 1]. Mean age of patients was 44.8 ± 10.2 years, ranging from 20 to 72 years. Eight patients (2.6%) developed DVT. All were male and were below 50 yr age. DVT confirmed by Duplex Doppler ultrasonography. [Figure 1].

DVT was present in six patients in alcoholic cirrhosis and two in HCV related cirrhosis [Table 1]. Alcoholic liver disease accounted for more than 82% of patients with liver cirrhosis. Hepatic encephalopathy was found in about 12.6% cases whereas 75% of the patients presented with ascites on admission, [Table 1]. Data analysis showed that protein was low universally in all cirrhotic patients however serum albumin level was significantly low (1.96 +0.11, P<.001) in the DVT group [Table 2].

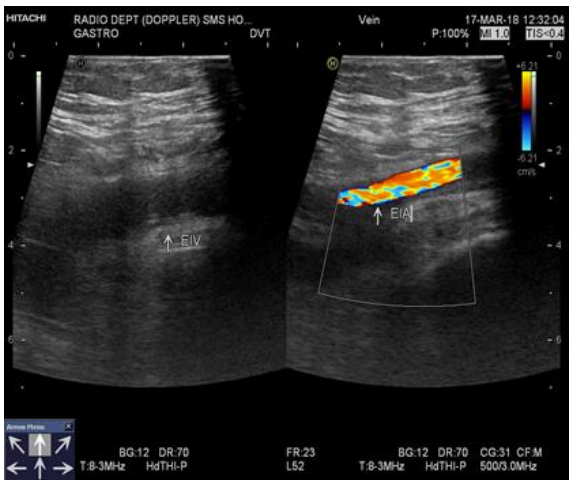

Figure 1: Doppler ultrasonography of a cirrhotic patient with deep vein thrombosis

Presence of ascites in DVT group was not significant and none of the patient with encephalopathy found in DVT group. Six DVT patients had child B cirrhosis and two had child cirrhosis [Table 1] none of the patient with DVT had encephalopathy.

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CTP and Na MELD value in both DVT and non DVT groups was not significant. No other malignancy including HCC was found in DVT patient. Seven patients had malignancy in non DVT group. No significant difference of laboratory parameters (i.e., serum liver enzymes, total bilirubin, platelets count, and prothrombin time) was found between the two groups [Table 2]. Several clinical variables, such as sex, age group, aetiology, diabetes mellitus, and hepatocellular carcinoma, were analysed [Table 3]. Other risk factors, such as inherited hypercoagulable states were measured, and all had low value in DVT group. Alcohol aetiology was higher in the group of cirrhotic patients with DVT, but it failed to reach statistical significance.

Serum albumin was the only variable significantly associated with the presence of DVT which tended to be a risk factor with a near-significant 95% confidence interval. Other risk factor smoking, obesity, dyslipidaemia was not measured.

Table 1: Clinical characteristic of cirrhotic patients with and without DVT.

Characteristics		DVT (+)	DVT (-)	Total	P value	Significance
Sex	Male	8(2.67)	280(93.33)	288(96.00)	>.05	NS
	Female	0(0.00)	12(4.00)	12(4.00)	>.05	NS
Age group (In Yrs)	<50	8(2.67)	182(60.07)	190(63.33)	>.05	NS
	>50	0(0.56)	110(36.67)	110(36.67)	>.05	NS
Etiological group	NV	6(2.00)	259(86.33)	265(104.00)	>.05	NS
	V	2(0.67)	33(1.00)	35(11.67)	>.05	NS
Ascites	Yes	6(2.00)	225(75.00)	231(77.00)	>.05	NS
	no	2(0.67)	67(22.33)	69(23.00)	>.05	NS
Encephalopathy	Yes	0(0.00)	38(12.67)	38(12.11)	>.05	NS
	No	8(2.67)	254(84.67)	262(87.89)	>.05	NS
Type 2 diabetes	Yes	0(0.00)	17(5.67)	17(5.67)	>.05	NS
	No	8(2.67)	275(91.67)	283(94.33)	>.05	NS
HCC	Yes	0(0.00)	7(2.33)	7(2.33)	>.05	NS
	No	8(2.67)	285(95.00)	293(97.67)	>.05	NS
CTP score	B	6(2.00)	187(66.20)	193(62.33)	>.05	NS
	C	2(0.67)	105(31.83)	107(35.67)	>.05	NS

Table 2: Laboratory values of cirrhotic patients with and without deep vein thrombosis (DVT)

Parameters	Mean + SD		P-value
	DVT +ve (N=8)	DTV –ve (N=292)	
T. Bilirubin	4.23 + 2.46	4.98 + 4.97	> .05
Platelet	0.83 + 0.40	1.27 + 5.47	> .05
AST	129.75 + 49.55	123.16 + 71.69	> .05
ALT	61.12 + 31.16	55.11 + 44.63	> .05
S. albumin	1.96 + 0.11	3.11 + 0.24	< .001**
ALP	134.37 + 80.61	114.56 + 71.29	> .05
GGT	184.50 + 76.67	206.52 + 148.96	> .05
MELD-Na	24.62 + 2.34	24.62 + 7.72	> .05
PT	22.8+ 4.5	21 ± 5.3	>.05

Table 3: Etiological spectrum of liver cirrhosis in DVT and non DVT group.

Aetiology	DVT (+)	DVT (-)	Total
Autoimmune hepatitis (AIH)	-	5	5
Alcohol consumption (Alc)	6	240	246
Alc + hbv	-	3	3
Alc + Wilson	-	1	1
HBV	-	23	23
Hcv	2	9	11
Nash	-	7	7
Nash/hbv	-	1	1
Unknown	-	1	1
Wilson ds.	-	2	2
Total	8	292	300

DISCUSSION

Chronic liver disease has been predominantly considered to be associated with coagulopathy and bleeding tendencies. More recently it has been discovered that patients with cirrhosis are in a rebalanced state of coagulation with alteration in both pro- and anti-coagulation factors.10 Though chronic liver disease is associated with increased risk of bleeding, there is increasing evidence to suggest that the risk of thrombosis is not to be discounted in these patients.

In patients with liver cirrhosis venous thromboembolism is considered a rare event, with unpredictable course and unclear mechanism. There are very few studies in India regarding DVT in liver cirrhosis available, comparing our results with the studies in Asia and west6, we found that the incidence of DVT was 2.67 % in our series. In one of the studies found that 113 cirrhotic patients out of more than 21000 cirrhotic admissions over8-year

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period developed VTE, with predominant viral and non-alcoholic steatohepatitis aetiology giving the incidence of about 0.5%.[7]

Another study done by Harjot Shah et al11 in 2021, found that the incidence of thrombosis was 4 % (6 / 150) with 3.33 % for portal vein / splanchnic thrombosis and 0.33 % for non-splanchnic venous thrombosis. There was no de novo thrombosis in the study cohort over a 3 month follow-up period. Portal vein thrombosis is a known complication of cirrhosis. The mean age of patients with thrombosis 44.8 ± 10.2 years as compared to other studies done by Harjot Shah et al,[11] Lizarraga et al,[12] and Northup et al,[7] reported mean age of 46.0, 56.2 and 54.6 years respectively.

As compared to this study in our study alcohol was the predominant cause of cirrhosis in six out of eight (82%) patients. We did not find any association between the clinical factors, such as sex, age, and various laboratory findings with the presence of DVT in liver cirrhotic patients except most of our cirrhotic patients had low serum albumin level (i.e., less than the normal cut off point of 3.5 mg/dl), however albumin was significantly low in the DVT group. Various studies suggest that low albumin level may indicate an advanced liver disease and may be used as an indirect marker for the levels of other proteins produced by the liver.[13-15] It can be taken as suggestive risk factor for development of DVT in cirrhotic patients. Other factors, such as protein C, protein S, and anti-thrombin III were found low in DVT patients in our study, however in liver disease their concentrations decrease (but not lower than 20% of normal), could be the risk factor for developing DVT. DVT was found in two patient of HCV related cirrhosis in our study, this finding was supported by another study16 that the risk of DVT is significantly higher in the HCV group than in the non-HCV group (adjusted HR=1.96;95% CI=1.03-3.73) and hepatitis C infection could be a risk factor of DVT in patients with liver cirrhosis. The potential disease state favouring DVT or PE in patients with liver cirrhosis could be an imbalance of clotting cascade favouring coagulation, immobility of end stage liver disease, infection, and systemic inflammation.[17]

A study done by Harjot Shah et al11 found that the aetiology of liver disease in study population was alcoholic liver disease (52 %), hepatitis C (12 %), NAFLD (11.3 %), hepatitis B (6 %) and alcoholic liver disease with hepatitis C (6 %). Another study done by Northup et al.[7] Lizarraga et al,[12] and a multi-centre Indian study by Mukherjee et al,[18] done to delineate the etiological profile of chronic liver disease, which was compatible with our results.

Immobilization during hospital stay is known as a risk factor for venous thrombosis due to the stasis of blood flow in the venous system. Therefore, patients with cirrhosis may share the same risk as other hospitalized patients. However, in our study colour Doppler of patient was done on next day after admission and the risk of thrombosis has been suggested when the length of hospital stay is more than 4 days.[19]

Cancer is a known risk factor of thrombosis and the risk of thrombosis in patients with cancer also increases with the use of chemotherapy, hormonal therapy, and indwelling central venous catheters and may increase by 4 to 6 folds. In our study none of the patient had malignancy in DVT group.20HCC was not found in patient in DVT group in our study inspite it was found in 7 patients out of 292 patients (2.3%) in non DVT group.

Limitation of the study

DVT patients were not assessed for DVT risks at admission like inherited hypercoagulable states (e.g. factor V Leiden, prothrombin gene mutation), Therefore we could not rule out the possibility of other risk factors that might contribute to the presence of DVT in our study.

CONCLUSION

The prevalence of DVT in patients with liver cirrhosis was 2.6% in our study. Hypoalbuminemia was the only risk factor for developing DVT found in this study and further studies on the mechanisms and prevention of DVT needed in future.

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