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A Study of Plasma D-Dimer Levels in Various Stages of Liver Disease

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Abstract

Aim: Defects in the process of coagulation and fibrinolysis is a common feature of various types of liver disease. The present study sought to evaluate the utility of D Dimer, a stable product of fibrinolysis in assessing this aspect of liver function. In the present study we estimated the D-Dimer levels to determine the status of coagulation defect and bleeding tendency.

Materials and methods: Ninety-nine patients with chronic liver disease were classified into groups A, B and C based upon the Child-Pugh scores. This score was calculated based upon values of serum bilirubin, serum albumin, internationalized normal ratio (INR), as well the severity of ascitis and hepatic encephalopathy. Plasma D-Dimer was estimated using an immuno-turbidimetry. The results were analyzed using the student's 't' test as well as ANOVA.

Results: The plasma D-Dimer levels were found to be increased significantly with severity of liver disease ($p<0.005$). Prothrombin time and INR increased significantly while fibrinogen decreased significantly from A to C groups ($p<0.05$).

Conclusion: Apart from coagulation defects, increased fibrinolytic activity could be one of the important factors responsible for the bleeding tendency in liver disease. D- Dimer can therefore be looked upon as an important parameter for the assessment of fibrinolytic status in chronic liver disease. It should be used in conjunction with the parameters of coagulation in order to assess the bleeding tendency in these patients.

Keywords: D-Dimer; Fibrinogen; PT; Child-Pugh score; Coagulation defects; Liver disease

Introduction

Hemostasis is a balance between pro-coagulant and anti-coagulant forces [1]. The liver is the site of synthesis of several proteins which are involved in the process of coagulation such as prothrombin and fibrinogen [2,3]. Liver function tests include standard laboratory tests to help in the evaluation of coagulopathy in liver disease. The determination of prothrombin time (PT) or international normalized ratio (INR), activated partial thromboplastin time (APTT), and fibrinogen are generally carried out in order to assess the coagulation status of patients with chronic liver disease. This becomes particularly important when a patient with a history of chronic liver disease has to undergo any surgery, in order to assess the risk of bleeding.

While there are several tests which assess the coagulation status tests there are no tests which are routinely carried out in order to assess the fibrinolytic status, a process which can have an impact upon the bleeding tendency of these patients. Coagulation followed by fibrinolytic activity leads to a fall in the levels of fibrinogen with a concomitant rise in the levels of fibrin degradation products [FDP's] [4]. D-Dimer is a stable and measurable parameter formed by the enzymatic breakdown of the cross-linked fibrin. Estimation of D-Dimer has hitherto been used for the diagnosis of conditions such as deep vein thrombosis and pulmonary embolism [5,6]. Since chronic liver disease is associated with disordered hemostasis, it is possible that it could be associated not only with defects in coagulation but also of clot lysis. Estimation of D –Dimer might provide some insight into possible derangements in the fibrinolytic pathway.

Aims and Objectives

This study was carried out in order to determine whether plasma D Dimer levels were abnormal in patients with an established diagnosis of liver disease. It also sought to ascertain whether there was a statistically significant difference in the D Dimer levels between the three groups of patients when they were classified on the basis of the Child-Pugh score.

The Child-Pugh score is an internationally accepted system for grading the severity of chronic liver disease such as cirrhosis.

Material and Methods

The study was approved by the Institutional Human Ethics Committee.

Subjects

The study population consisted of ninety-nine adult male patients admitted into the gastro-enterology unit of PSG Hospitals, Coimbatore. All these patients had an established diagnosis of chronic liver disease. Patients with evidence of renal disease were excluded from the study. The case sheets of these patients were studied in order to confirm the diagnosis and grade their severity. They were classified into three groups A, B and C using the Child-Pugh scoring system which has been indicated in Table 1 and 2.

All the biochemical parameters were assayed using Roche Cobas

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Integra 400 plus autoanalyser. The veracity of the methodology was ensured by running Bio-Rad quality control samples on a regular basis. D-Dimer was also estimated using Cobas Integra 400 plus using particle-enhanced immuno-turbidimetry.

Statistical Analysis

Student-'*t*' test and one way ANOVA (Table 5) was used to compare the results of the three groups. A 'p' value was less than 0.05 was considered to be statistically significant.

Results

The results are as shown in Table 3 and 4 and the Figure 1 and 2. Plasma D-Dimer levels were found to increase significantly with severity of liver disease. There was also a significant increase in both PT and INR and a fall in fibrinogen between the three groups. The 'p' values between different groups are shown in Table 2.

Discussion

Patients with liver cirrhosis have a bleeding tendency that is often not evident from routine coagulation tests. In such patients, the incidence of hyperfibrinolysis varies from 19% to 95% [7-11] and may contribute to serious bleeding complications. The pathogenesis of hyperfibrinolysis in liver cirrhosis is not yet clearly known.

In the present study plasma D-Dimer levels were found to increase significantly with severity of liver disease. PT and INR also increased significantly while fibrinogen decreased significantly from A to C groups. The results have clearly shown that patients with chronic liver disease have a combination of both defective coagulation and accelerated fibrinolysis. Our finding is in agreement with that of Agarwal et al who reported increased plasma D-Dimer in 63% of patients with liver cirrhosis [12].

Hyperfibrinolysis in liver disease is said to be due to decreased clearance of tissue plasminogen activator (tPA). Tissue plasminogen activator catalyses the conversion of plasminogen to plasmin and the subsequent breakdown of fibrin clot. In health, tPA is bound to its inhibitor plasminogen activator inhibitor (PAI-1) which limits the effect of circulating tPA. High circulation levels of tPA have been described in cirrhotics especially those with alcoholic cirrhosis and this coupled with the decreased hepatic synthesis of PAI-1, leads to activation of fibrinolysis. Chronic liver disease is known to be associated with increased levels of tPA due to enhanced release by the activated endothelium and/or by reduced clearance by the diseased liver (or) decreased levels of anti-plasminogen activators (PAI). This could be aggravated by the decreased synthesis of fibrinolytic inhibiting factors. This is finally manifested in the form of increased D-Dimer levels which is a measurable parameter for assessing the entire fibrinolytic system [13-15].

Child-Pugh Measure	1 point	2 points	3 points	Units
Serum total Bilirubin	<2	2-3	>3	mg/dL
Serum albumin	>35	28-35	<28	G/dL
INR	<1.7	1.71-2.20	> 2.20	no unit
Presence of Ascites	None	Suppressed with medication	Refractory	no unit
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	no unit

Table 1: Criteria for Child-Pugh Score [7,8].

Points gained	5-6	7-9	10-15
Child –Pugh Class	A	B	C

Table 2: Interpretation. Chronic liver disease is further classified into Child-Pugh class A to C, by employing the added score from above.

LFT	Group A (n=16)	Group B (n=62)	Group C (n=21)	Units
D Dimer	3.26 (± 2.77)	5.52 (± 2.92)	6.81 (± 2.86)	µg FEU/mL
Fibrinogen	265 (± 113)	205 (± 86)	156 (± 90)	mg/dL
Bilirubin	1.04 (± 1.08)	3.18 (± 5.82)	10.2 (± 8.86)	mg/dL
Albumin	3.29 (± 0.58)	2.6 (± 0.64)	2.43 (0.65)	g/dL
PT	16 (± 3)	21 (±10)	41.5 (± 40)	Seconds
INR	1.3 (± 0.25)	2 (± 1.25)	3 (± 1.22)	

Table 3: Showing average values of different LFT parameters.

	D-Dimer	Fibrinogen	PT	Albumin	Bilirubin
Group A vs. B	< 0.05*	<0.0005*	<0.005*	<0.0001*	<0.05*
Group B vs. C	<0.2	<0.05*	<0.05*	>0.2	<0.005*
Group A vs. C	<0.05*	<0.0005*	<0.1	<0.0001*	<0.005*

Table 4: Showing 'p' values between different groups.

LFT	Group A (n=16)	Group B (n=62)	Group C (n=21)	p Value
D Dimer (µg FEU/mL)	3.26 (±2.77)	5.52 (± 2.92)	6.81 (± 2.86)	0.001*
Fibrinogen (mg/dL)	265 (± 113)	205 (± 86)	156 (± 90)	0.002*
Bilirubin (mg/dL)	1.04 (± 1.08)	3.18 (± 5.82)	10.2 (± 8.86)	0.000*
Albumin (g/dL)	3.29 (± 0.58)	2.6 (± 0.64)	2.43 (0.65)	0.000*
PT (seconds)	16 (± 3)	21 (±10)	41.5 (± 40)	0.000*
INR	1.3 (± 0.25)	2 (± 1.25)	3 (± 1.22)	0.000*

Table 5: ANOVA for three deferent Child Pugh Classes.

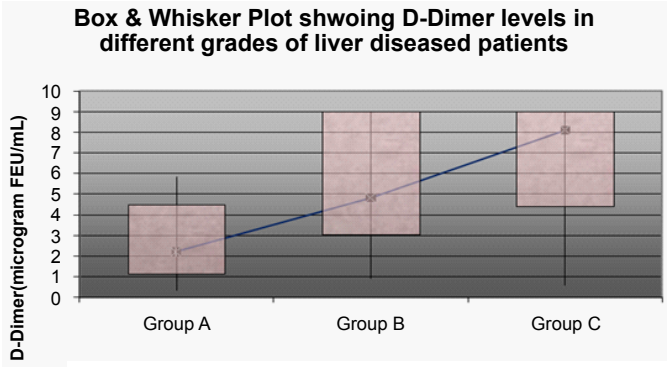

Figure 1: Box & Whisker Plot Showing D-Dimer Levels in Dfferent Grades of Liver Disease Patients.

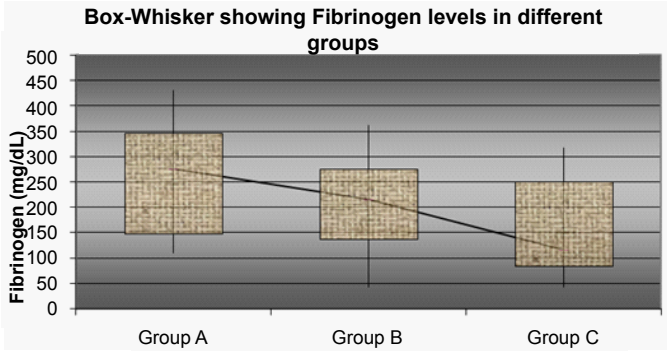

Figure 2: Box & Whisker Showing Fibrinogen Levls in Different Groups.

Conclusion

Apart from coagulation defects, increased fibrinolytic activity could be one of the important factors responsible for the bleeding tendency in liver disease. D-Dimer can therefore be looked upon as an important parameter for the assessment of fibrinolytic status in chronic liver disease. It should be used in conjunction with the parameters of coagulation in order to assess the bleeding tendency in these patients.

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