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Prothrombin Time and Activated Partial Thromboplastin Time in Case of Liver Disease- A Study of 100 Cases.

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ABSTRACT

Background: Prothrombin Time is a measure of the integrity of extrinsic and final common pathways of the coagulation cascade while aPTT is a measure of the integrity of intrinsic and final common pathways of the coagulation cascade.Our study has demonstrated the effect of liver disease on both Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT), and the risk of bleeding in these patients on the basis of these parameters. Aims: To correlate the effect of liver disease on PT&aPTT and to evaluate the risk of bleeding in these patients on the basis of these parameters. **Methods:** Blood samples of patients with preliminary diagnosis of liver disease were collected in 3.2% sodium citrate (9 parts blood and 1 part sodium citrate). PT was measured using thromboplastin reagent and aPTT was measured using cephaloplastin reagent. **Results:** Coagulation parameters PT and aPTT are prolonged and platelet counts are decreased more frequently in cases of cirrhosis (chronic liver disease) and less frequently in cases of hepatitis and other liver diseases. Patients of cirrhosis who had prolongation of PT, aPTT or decreased PC had more chances of gastrointestinal bleeding as compared to those who had normal values of these parameters. **Conclusion:** Coagulation parameters PT and aPTT can be used to predict the amount of damage to synthetic capacity of liver in liver diseases, also to predict the risk of bleeding in case of chronic liver diseases.

Keywords: Prothrombin Time, activated Partial Thromboplastin Time, Platelet count, Liver disease, Risk of bleeding.

INTRODUCTION

PT was discovered by Dr. Armand Quick and colleagues in 1935.[1] aPTT was first described by researchers at University of North Carolina at Chapel Hill.[2]

Prothrombin Time is a measure of the integrity of extrinsic and final common pathways of the coagulation cascade. This consists of tissue factor and factors VII, II, V, X and fibrinogen.[3] This test bypasses the intrinsic pathway and the factors involved therein. Because tissue thromboplastins contain phospholipids that act as platelet substitutes, the test is unaffected by platelet numbers. Reference range of PT is 11 to 16 seconds.[4]

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aPTT is a measure of the integrity of intrinsic and final common pathways of the coagulation cascade. When a mixture of plasma and phospholipid platelet substitute is recalcified, fibrin forms at a normal rate only if the factors involved in intrinsic pathway (prekallikrein, high-molecular-weight kininogen, and factors XII, XI, IX and VIII) and in the common pathway(factors X and V, prothrombin and fibrinogen) are present in normal amounts. aPTT bypasses the extrinsic pathway. Reference range for aPTT is 26 to 40 seconds at 3 minutes activation time.[5]

When both PT & aPTT are prolonged, defect is probably in the common clotting pathway, and a deficiency of factor I, II, V or X is suggested. A normal PT with an abnormal aPTT means that defect lies in the intrinsic pathway. A normal aPTT with an abnormal PT means that defect lies within the extrinsic pathway & suggests a possible factor VII deficiency.

Causes of prolonged PT

- Warfarin Use
- Vitamin K deficiency from malnutrition, biliary obstruction, malabsorption syndromes or use of antibiotics.

- Liver disease due to diminished synthesis of clotting factors.
- Deficiency or presence of an inhibitor to fator VII, X, II, V or fibrinogen.
- DIC
- Fibrinogen Abnormality (eg Hypofibrinogenemia, afibrogenemia, dysfibrogenemia)
- After bolus administration of heparin (PT may be transiently elevated)
- Massive blood transfusion due to dilution of clotting proteins.
- Hypothermia, as it causes inhibition of a series of enzymatic reactions of coagulation cascade.[6]

PT has good correlation with severity of liver disease. Profound hepatic synthetic dysfunction is the hallmark of Acute Liver Failure with resulting metabolic disarray and highly abnormal PT.[7]

Causes of prolonged aPTT

- Congenital deficiencies of intrinsic system clotting factors such as VIII, IX, XI, XII including Hemophilia A and Hemophilia B
- Congenital deficiency of Fitzgerald factor (Prekallikrein)
- Von Willebrand Disease
- Hypofibrinogenemia
- Liver Cirrhosis
- Vitamin K deficiency
- DIC
- Heparin therapy
- Coumarin therapy
- Non-specific inhibitors such as lupus anticoagulant & anticardiolipin antibodies which bind to phospholipids and surface of platelets.
- Specific circulating anticoagulants such as SLE, RA, TB & Chronic Glomerulonephritis.[8,9]

Abnormalities Of Hemostasis & Coagulation In Liver Disease.[10,11]

Deficient biosynthesis

- Of fibrinogen, prothrombin, coagulation factors V, VII, IX, X, XI, XII, XIII, prekallikrein, high-molecular-weight kininogen
- Of antiplasmins, antithrombin, proteins C & S Aberrant biosynthesis
- Of abnormal fibrinogen,[12] factor V
- Of abnormal inhibitory analogs of prothrombin, factors VII, IX, X.[13]

Deficient clearance

- Of hemostataic “products” (e.g fibrin monomers, fibrinogen degradation products, platelet factor-3)
- Of activated coagulation factors (IXa, Xa, Xia)
- Of plasminogen activators

Accelerated destruction of coagulation factors

- Disseminated Intravascular Coagulation.[14]
- Abnormal fibrinolysis

Thrombocytopenia

- Hypersplenism (portal hypertension)
- Folic Acid deficiency
- Chronic ethanol intoxication
- Disseminated intravascular Coagulation

Platelet dysfunction

- Acute and Chronic ethanol intoxication
- Effects of products fibrinogen degradation.[15]
- Uremia

Miscellaneous

- Inhibition of coagulation by products of fibrinogen degradation.[16]
- Loss or consumption of coagulation factors in ascitic fluid.

In patients with liver disease, all coagulation factors except factor VIII may be deficient as a consequence of synthetic failure of the hepatic cells. Deficiencies of prothrombin, factors VII, IX, X and protein C & S result mainly from synthetic incompetence.

Endogenous plasminogen activators normally are removed from the circulation by the liver. In patient with severe liver disease, however, they may circulate for an abnormally long time and lead to the chronic or intermittent activation of the fibrinolytic enzyme system. This process may be a contributory factor, in the pathogenesis of hypofibrinogenemia in patients with liver disease. It also leads to the production of large amount of fibrinogen degradation products, which persist in the circulation for abnormally long periods because of deficient hepatic clearance, and may impair blood coagulation and platelet function.[15]

MATERIALS AND METHODS

The study was done on 100 patients of liver disease presenting in the Department of Medicine. PT and aPTT measurements were done in the clinical laboratory.

Inclusion criteria

Patients with preliminary diagnosis of hepatitis, alcoholic liver disease, cirrhosis and other liver diseases were included in the study.

Exclusion criteria

Patients with inherent bleeding tendencies, e.g., due to congenital deficiency of coagulation factors, & those already known to have antiphospholipid antibodies in plasma were excluded from the study.

Method of PT measurement

PT is measured by Quick's method. Reagent used in PT testing is thromboplastin.

Principle

When anticoagulated plasma is added to rabbit brain thromboplastin in the presence of calcium, extrinsic pathway gets activated. Consequently, thrombin is generated resulting in the formation of fibrin and hence clot formation. The time in seconds taken for the formation of fibrin clot is measured as PT.[17,18]

Normal value for PT was taken between 12 & 16 seconds.

Method of aPTT measurement

We used activated cephaloplastin reagent for determination of aPTT. It is a phospholipid preparation derived from rabbit brain with elagic acid as an activator.

Principle

Cephaloplastin activates the coagulation factors of the intrinsic pathway of coagulation mechanism in the presence of calcium ions. aPTT is prolonged by the deficiency of one or more of these clotting factors of intrinsic pathway and in the presence of coagulation inhibitors like heparin.

Normal values using cephaloplastin reagent are taken between 22 to 34 seconds at 3 minutes.[19,20]

RESULTS

Total 100 patients with liver disease enrolled for the study were categorized into 3 categories- a) patients with cirrhosis (49), b) patients with hepatitis (44), and c) patients with other liver diseases (07).

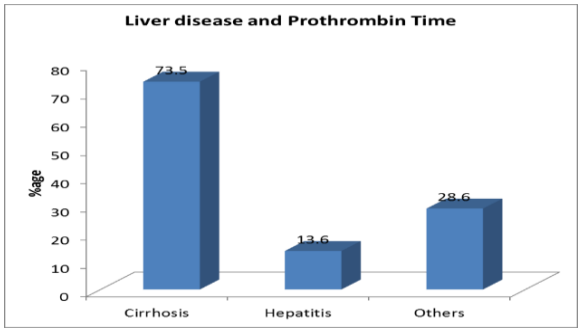
Among 100 patients of liver disease, 49 had cirrhosis, 44 had hepatitis (including hepatitis A, hepatitis B, alcoholic hepatitis), and rest 7 had other liver diseases including liver abscess, hepatocellular carcinoma, etc. 74 were males and 26 were females.

Mean age of patients with cirrhosis was 51.98±11 years. Mean age of patients with hepatitis and with other liver diseases was 50.52±15.4 years and 47±14 years respectively.

Among patients of cirrhosis, mean platelet count was 1,33,234±63948/µL of blood, while among patients of hepatitis and other liver diseases, it was 1,94,068±76081/µL of blood and 1,68,571±30237/µL of blood respectively. Statistical analysis shows a p value of <0.001 suggesting a highly significant association of decreased platelet count (PC) with cirrhosis.

Table 1: Liver disease and Prothrombin Time.

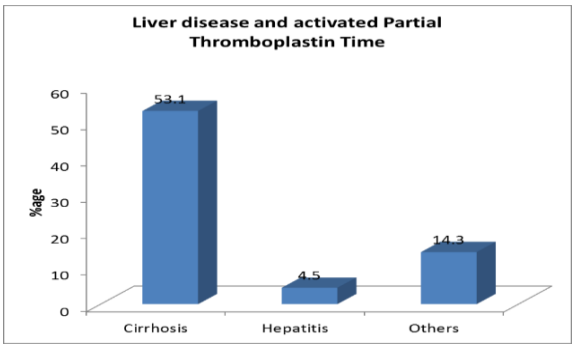
Liver disease	Total no. of patients	No. of patients with abnormal PT	Percentage (%)	No. of patients with normal PT	Percentage (%)
Cirrhosis	49	36	73.5	13	26.5
Hepatitis	44	06	13.6	38	86.4
Others	07	02	28.6	05	71.4



Out of 49 cases of cirrhosis, PT is raised in 36 cases, out of 44 cases of hepatitis, PT is raised in 6 cases, and out of 7 cases of other liver diseases, PT is raised in 2 cases. Statistical analysis shows a p value of <0.001 in case of cirrhosis which is highly significant. [Table 1]

Table 2: Liver disease and activated Partial Thromboplastin Time.

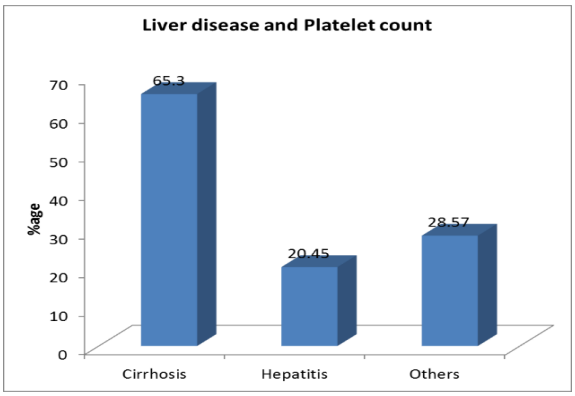
Liver disease	Total no. of patients	No. of patients with abnormal aPTT	Percentage (%)	No. of patients with normal aPTT	Percentage (%)
Cirrhosis	49	26	53.1	23	46.9
Hepatitis	44	02	4.5	42	95.5
Others	07	01	14.3	06	85.7



Out of 49 cases of cirrhosis, aPTT is raised in 26 cases, out of 44 cases of hepatitis, aPTT is raised in 2 cases, and out of 7 cases of other liver diseases, aPTT is raised in 1 case. Statistical analysis shows a p value of< 0.001 in case of cirrhosis which is highly significant. [Table 2]

Table 3: Liver disease and Platelet count.

Liver disease	Total no. of patients	No. of patients with abnormal PC	Percentage (%)	No. of patients with normal PC	Percentage (%)
Cirrhosis	49	32	65.3	17	34.7
Hepatitis	44	9	20.45	35	79.54
Others	07	02	28.57	05	71.4



Out of 49 cases of cirrhosis, PC is abnormally low in 32 cases, out of 44 cases of hepatitis, PC is abnormally low in 9 cases, and out of 7 cases of other liver diseases, PC is abnormally low in 2 cases. Statistical analysis shows a p value of <0.001 in case of cirrhosis which is highly significant. [Table 3]

Out of 49 cases of cirrhosis, both PT and aPTT are raised in 24 cases, out of 44 cases of hepatitis, both PT and aPTT are raised in 1 case, and out of 7 cases of other liver diseases, both PT and aPTT are raised in 1 case. Statistical analysis shows a p value of <0.001 in case of cirrhosis which is highly significant.

Table 4: Prothrombin time and Gastrointestinal bleeding.

Abnormal PT	**Total**	44
	Bleeding+	28
	Bleeding -	16
Normal PT	Total	56
	Bleeding+	05
	Bleeding -	51

Out of 44 cases with prolonged PT, 28 had bleeding, while out of 56 cases of normal PT, only 5 had bleeding. Statistical analysis shows a p value of <0.001 showing highly significant association of prolonged PT with risk of gastrointestinal bleeding. [Table 4]

Table 5: Activated Partial Thromboplastin Time and Gastrointestinal bleeding.

Abnormal aPTT	**Total**	29
	Bleeding+	22
	Bleeding -	07
Normal Aptt	Total	71
	Bleeding+	11
	Bleeding -	60

Out of 29 cases with prolonged aPTT, 22 had bleeding, while out of 71 cases of normal aPTT, 11 had bleeding. Statistical analysis shows a p value of <0.001 showing highly significant association of prolonged aPTT with risk of gastrointestinal bleeding. [Table 5]

Table 6: Platelet count and Gastrointestinal bleeding.

Platelet count	Total	Bleeding+	Bleeding-
Abnormal	43	25	18
Normal	57	08	49

Out of 43 cases with decreased PC, 25 had bleeding, while out of 57 cases of normal PC, 8 had bleeding. Statistical analysis shows a p value of <0.001 showing highly significant association of decreased PC with risk of gastrointestinal bleeding. [Table 6]

DISCUSSION

The various studies done in patients of different liver diseases have shown variable percentages of patients with prolongation of PT, aPTT and PC. Table 7 shows the frequency of alteration of these parameters in different studies. [Table 7]

Table 7: Comparison of frequancy of abnormal PT, aPTT and PC in cirrhosis in various studies.

Study	Altered PT (% of cases)	Altered aPTT (% of cases)	Altered PC (% of cases)
Zafar MN et al[21]	54	16	-
Siddiqui SA et al[22]	87.7	71.3	36.8
Nwokediuko SC et al[23]	36.6	22.6	42.7
van Nieuwenhuizen RC et al[24]	79	42	11
Devrajani BR et al[25]	50.85	51.7	-
Shah Shaila et al[26]	52	62	48
Present study	73.5	53	65.3

Table 8: Comparison of coagulation parameters in Cirrhotic patients with bleeding.

Study	Total no. of cirrhotics with bleeding	Abnormal PT	Abnormal aPTT	Abnormal PC
Shah Shaila et al[26]	28	20	23	18
Present	31	27	22	23

Table 9: Comparison of coagulation profile in patients with cirrhosis.

Study	No. of cases with cirrhosis	Prolonged PT	Prolonged aPTT	Prolonged PT, aPTT both
Zafar MN et al[21]	50	27 (54%)	08 (16%)	04 (8%)
Siddiqui SA[22]	171	87.7%	71.3%	67%
Present	49	36 (73.5%)	26 (53.1%)	24 (48.98%)

In the present study, 31 out of 49 patients of cirrhosis had bleeding. Out of these 31 patients, 27 (87.1%) had prolonged PT, 22 (70.97%) had prolonged aPTT, and 23 (74.19%) had abnormally low PC ('p' value of <0.001 in all three parameters). Similar results were obtained in study done by Shah Shaila et al where out of 28 patients of cirrhosis who had bleeding, PT was prolonged in 20 (71.43%) patients, aPTT in 23 (82.14%) patients, and PC was abnormally low in 18 (64.29%) patients ('p'values of <0.05 in all three parameters). [Table 8]

In the present study, 1 patient of hepatitis who had bleeding, had normal PT as well as aPTT, while PC was abnormally low. In the study by Shah Shaila et al out of 4 patients of hepatitis who had bleeding, 2 had prolonged PT, 3 had prolonged aPTT, and 2 had abnormally low PC. 'p' values in all parameters in

both the studies were >0.05 showing an insignificant association of hepatitis who had bleeding with PT, aPTT and PC.

In the present study, 1 patient of other liver diseases who had bleeding, had prolonged PT, normal aPTT, and abnormally low PC. In study by Shah Shaila et al out of 5 patients of other liver diseases who had bleeding, 4 had prolonged PT, prolonged aPTT, and abnormally low PC. 'p' values in all parameters in both the studies were >0.05 showing an insignificant association of other liver diseases who had bleeding with PT, aPTT and PC.

Out of 49 patients of cirrhosis in the present study, 36 (73.5%) had prolonged PT, 26 (53.1%) had prolonged aPTT, and 24 (48.98%) had prolongation of both PT&aPTT. In similar studies done by Siddiqui SA et al and Zafar MN et al, results obtained differed. In study done by Siddiqui SA et al, 87.7% out of 171 cases of chronic liver disease had prolonged PT, 71.3% had prolonged aPTT, and 67% had prolongation of both PT&aPTT. While in the study done by Zafar MN et al out of 50 patients of cirrhosis, 27 (54%) had prolonged PT, 08 (16%) had prolonged aPTT, and 04 (8%) had prolongation of both PT&aPTT. [Table 9]

In the present study, 28 (63.63%) out of 44 patients with prolonged PT, 22 (75.86%) out of 29 patients with prolonged aPTT and 25 (58.14%) out of 43 patients with abnormally low PC had bleeding. In study done by Shah Shaila et al, similar results were obtained with 35 (76.09%) out of 46 patients with prolonged PT, 43 (74.14%) out of 58 patients with prolonged aPTT and 28 (75.68%) out of 37 patients with abnormally low PC having bleeding.

CONCLUSION

In the present study conducted among 100 patients of liver disease, it was seen that PT was prolonged more frequently in patients of liver disease as compared to aPTT.

Coagulation parameters PT and aPTT are prolonged and platelet counts are decreased more frequently in cases of cirrhosis (chronic liver disease) and less frequently in cases of hepatitis and other liver diseases.

Patients of cirrhosis who had prolongation of PT, aPTT or decreased PC had more chances of gastrointestinal bleeding as compared to those who had normal values of these parameters.

Alteration of these coagulation parameters in patients of liver diseases is not associated with age, hemoglobin or serum bilirubin levels in the patients.

Thus coagulation parameters PT and aPTT can be used to predict the amount of damage to synthetic capacity of liver in liver diseases, also to predict the risk of bleeding in case of chronic liver diseases.

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