FREQUENCY OF PROLONGED ACTIVATED PARTIAL THROMBOPLASTINE TIME (APTT) IN LIVER CIRRHOSIS.

MUKAMIL SHAH¹, ABDUL AHAD², IMRAN UD DIN KHATTAK¹

1. Department of Pathology , Saidu Medical College, Saidu Sharif, Swat
2. Medicine Saidu Teaching Hospital, Saidu Sharif, Swat

ABSTRACT

BACKGROUND: Liver cirrhosis is very common disease in medical practice. Chronic Liver disease is marked by the gradual destruction of liver tissues over time. Severe liver disease falls under this category including cirrhosis of liver and fibrosis. Chronic damage to the liver slowly replaces normal functioning liver tissue, progressively diminish blood flow through the liver. As the normal liver tissue is lost, nutrients, hormones, drugs and poisons are not processed effectively by the liver. In addition protein production including coagulation factors and other substances produced by the liver are inhibited. This study was designed to find the relative frequency of having prolonged APTT in chronic liver disease.

STUDY DESIGN AND PLACE: This cross-sectional study of chronic liver disease was conducted in the departments of Medicine and Pathology of Saidu Teaching Hospital / Saidu Medical College, Swat, Pakistan from Feb 15th 2012 to Dec 15th 2012.

MATERIAL AND METHODS: Seventy eight (78) patients of chronic liver disease (38 Males & 40 Females) were studied. Those on anticoagulants therapy were excluded from the study. Ethylenediamine tetra acetic acid and citrated blood samples were taken for tests to be performed. Blood counts were performed on coulter counter haematology analyzer. APTT, Prothrombin time (PT), Bleeding time (BT) and thrombin time (TT) were performed manually.

RESULTS: Out of 78 patients of chronic liver disease, prolonged APTT was found in 64(82.05%) patients (28 males and 36 females). 14(17.95%) patients (10 males and 4 females) were found to have normal APTT.

CONCLUSION: Prolong APTT is significant finding in cirrhosis liver. It should be included in the investigations for bleeding tendencies of cirrhotic patients.

KEY WORDS: Activated partial thromboplastin time, chronic liver disease, cirrhosis liver.

INTRODUCTION

Liver cirrhosis is diffuse process in which the normal architecture of liver is converted into structurally abnormal nodules. In other words, it is the necrosis of the liver followed by fibrosis and regeneration. Its clinical features are produced by hepatocellular destruction, portal hypertension and Porto systemic shunting.¹ Liver cirrhosis leaves significant morbidity and mortality in our country, however early diagnosis prevents complications and carries good prognosis.²

Coagulation disorder in patients with liver disease results from impairment in the clotting and fibrinolytic system, and reduced number of platelets.³ As liver parenchymal cells synthesizes most of the clotting factors, levels of these procoagulants and anticoagulants as well as fibrinolytic and antifibrinolytic factors will decrease in plasma. These changes may be reflected in a minor way in patients with mild chronic liver disease. Thrombocytopenia usually complicate the clinical picture⁴. Chronic liver

disease especially cirrhosis liver is a major health problem in tropical countries like Pakistan.

This study was conducted to find the relative frequency of prolonged APTT in patients with this disease. It will help the hematologist in better understanding the severity of coagulation defects and their relative complications e.g. bleeding/thrombosis which will lead to better management of such patients^{5,6}.

SUBJECT AND METHODS

A total of 78 patients (38 males and 40 females) were included in this study. These patients were taken from Medical unit of Saidu Teaching Hospital/Saidu Medical College, Saidu Sharif, Swat, from Feb 15th, 2011 to Dec 15th, 2011. In each case a detailed history were taken. Thorough physical & clinical examination was performed.

A primary criterion of inclusion was the presence of cirrhosis liver, irrespective of etiology. Diagnosis of cirrhosis liver is based on a combination of

- a. Clinical features.
- b. Biochemical investigation.
- c. Abdominal ultrasound.

Cirrhotic patients with previous history of coagulation disorders and the drugs that causes changes in the coagulation parameters i.e. oral contraceptives, aspirin, heparin, warfarin were excluded.

All the investigations were performed at Saidu Medical College, Saidu Sharif, Swat Pakistan. EDTA and citrated blood samples were taken for tests to be performed. Blood counts performed on coulter counter haematology analyzer. BT, PT, APTT, TT were performed manually.

The statistical software SPSS version 15.0 was used for the analysis of data.

RESULTS

In this study 78 patients with liver cirrhosis were included. The patients were taken from Medical ward of Saidu Teaching Hospital Swat. Twenty

two normal individuals were included as control. APTT considered to be prolonged when the patient value was >10 seconds of control. The mean age of patients with cirrhosis was 57 years. The result of patients and controls are shown, in Tables: I, II & III. Table-I shows clinical features such as pallor in 70 (89.74%), ascites in 54(60.23%), edema in 50(64.10%), splenomegaly in 48(61.54%), jaundice in 39 (50.00%) and bleeding in 20(25.64%) patients.

Table-II shows biochemical investigations. PT was 26.84 ± 1.62 in 38 male patients and it was 13.10 ± 0.12 in 14 male controls with P value of < 0.01 . PT was 24.85 ± 2.37 in 40 female patients and it was 13.05 ± 0.15 in 8 female controls with p value of < 0.01 . APTT was 79.30 ± 4.20 in 38 male patients and it was 35.00 ± 0.23 in 14 male controls with p value of < 0.01 . APTT was 79.60 ± 13.60 in 14 female patients and it was 35.30 ± 0.30 in 8 female controls with P value of < 0.01 .

Thrombin Time (TT) was 12.47 ± 0.62 in 38 male patients and it was 10.0 ± 0.20 in 14 male controls with p value of < 0.05 .

Thrombin Time (TT) was 12.70 ± 0.98 in 40 female patients and it was 10.5 ± 0.23 in 8 female

Controls with p value of < 0.05 .

Bleeding Time (BT) was 5.00 ± 1.20 in 38 male patients and it was 6.30 ± 0.40 in 14 male controls.

Bleeding Time (BT) was 5.20 ± 0.73 in 40 female patients and it was 4.00 ± 0.45 in 8 female controls.

Table-III shows that Hb was 10.69 ± 0.40 in 38 male patients and it was 13.00 ± 0.20 in 40 male Controls with p value of < 0.001 .

Hb was 9.93 ± 0.82 in 40 female patients and it was 12.20 in female controls with P value of < 0.001 .

TLC $\times 10^6$ was 7.10 ± 0.95 in 38 male patients and it was 7.00 ± 0.40 in 14 male controls. TLC $\times 10^6$ was 7.8 ± 0.95 in 40 female patients and it was 6.40 ± 0.35 in 8 female controls. Platelet count $\times 10^6$ was 121 ± 8.07 in 38 male patients and it was 289 ± 10.0 in 14 male

Controls with p value of <0.001.

Platelet count $\times 10^6$ was 93.35 ± 12.0 in 40 female patients and it was 225 ± 13.0 in 8 female Controls with p value of <0.001.

MCV was 87.71 ± 3.28 in 38 male patients and it was 88.5 ± 4.0 in 14 male controls with P value <0.05.

MCV was 93.21 ± 2.70 in 40 female patients and it was 79.0 ± 6.0 in 8 female controls with P value < 0.05.

Table-I : Clinical Findings in Cirrhotic patients .

Pallor	Ascites	Edema	Spleno magly	Jaun dice	Bleedin g
70(89.7 4%)	54(69.2 3%)	50(64.1 0%)	48(61.5 4%)	39(5 0%)	20(25.6 4%)

Table-II: Prothrombin time, Activated Partial thromboplastin time, Thrombin time and Bleeding time of controls and patients.

Parameters	Gender	Controls	Patients	P Value
Prothrombine Time (PT) Sec	Male	(14) 13.10 ± 0.12	(38) 26.84 ± 1.62	p<0.01
	Female	(08) 13.05 ± 0.15	(40) 24.85 ± 2.37	p<0.01
Activated Partial Thromboplastin Time (APPT) Sec	Male	(14) 35.00 ± 0.23	(38) 79.30 ± 4.20	p<0.001
	Female	(08) 35.30 ± 0.30	(40) 79.60 ± 13.60	p<0.01
Thrombin Time (TT) Sec	Male	(14) 10.0 ± 0.20	(38) 12.47 ± 0.62	p<0.05
	Female	(08) 10.5 ± 0.23	(40) 12.70 ± 0.98	p<0.05
Bleeding Time (BT) minutes	Male	(14) 6.30 ± 0.40	(38) 5.00 ± 1.20	--
	Female	(08) 4.00 ± 0.45	(40) 5.20 ± 0.73	--

Table-III: Haemoglobin, Total Leucocytes Count (TLC), Platelets count and Mean corpuscular

Volume (MCV) in control and patients

Parameters	Gender	Control	Patients	P Value
Hb, (gm/dl)	Male	(14) 13.00 ± 0.20	(38) 10.69 ± 0.40	p<0.001
	Female	(08) 12.20 ± 0.24	(40) 9.93 ± 0.82	p<0.001
TLC $\times 10^6$	Male	(14) 7.00 ± 0.40	(38) 7.10 ± 0.95	--
	Female	(08) 6.40 ± 0.35	(40) 7.8 ± 0.95	--
Platelets Count $\times 10^6$	Male	(14) 280 ± 10.0	(38) 121 ± 8.07	p<0.001
	Female	(08) 225 ± 13.0	(40) 93.35 ± 12.0	p<0.001
MCV (fl)	Male	(14) 88.5 ± 4.0	(38) 87.71 ± 3.28	p<0.05
	Female	(08) 79.0 ± 6.0	(40) 93.21 ± 2.70	p<0.05

Activated partial thombopastin time was prolonged in 64 patients out of 78 (28 males & 36 females). 14 patients were found to have normal APTT.

Comparison of mean values of activated partial thrombopastin time for patients and controls are shown in table II. The difference of patients and control values in both patients and controls are statistically highly significant (P value < 0.001). The mean value in patients with cirrhosis was $121,000 \pm 8.07$ platelets/ cmm, which are significantly lower then the normal range of 150,000 – 450,000/ cmm.

The mean value in patients with cirrhosis was 10.00 ± 0.60 gm/dl which is significantly lower than the normal range of Hb 12 . 6 gm/dl.

DISCUSSION

Homeostasis is intimately related to liver functions, because most of coagulation factors

are synthesized in liver parenchymal cells and the liver's reticuloendothelial system carries an important role in the clearance of activated products. The extent of coagulation abnormalities depends upon the degree of disturbed liver functions⁷. Patients with cirrhosis suffer from a complex haemostatic disturbance, due to abnormalities in clotting and fibrinolytic system called secondary haemostasis.⁸

Platelet abnormalities associated with chronic liver disease include thrombocytopenia (decreased number of platelets) as well as abnormalities in function (thrombosthania) called primary haemostasis.⁹

In our study there was significant prolongation of activated partial Thromboplastin time in patients of liver cirrhosis. This finding is compatible with previous studies^{10, 11}. Prothrombin time is commonly increased in liver disease because liver is unable to manufacture adequate amount of clotting factors including those involved in extrinsic pathway.¹² Out of factor II, V, VII and X, factor VII is the rate limiting factor in this pathway and thus has greatest influence on the Prothrombin time. Fall of factor VII which has shortest half life (6 hours) has bad prognosis. As liver function worsens, the APTT prolongs, the reason being that factor IX, XI, XII and fibrin stabilizing factors are also produced by the liver.¹³ Prolongation of both PT and APTT may be noted while other biochemical tests of liver function in liver disease are still normal. Occasionally APTT may be abnormal when the PT is within normal range.¹⁴

In the present study platelets count was significantly decreased in the patients with hepatic cirrhosis. These findings are the same as reported in previous studies.¹⁵⁻¹⁶ Thrombocytopenia is common finding in patients with diagnosed liver disease.¹⁷ Severe thrombocytopenia < 30000 associated with spontaneous bleeding is usually not seen in uncomplicated cirrhosis. The common reason cited for Thrombocytopenia in patients with

cirrhosis is splenomegaly and portal hypertension.¹⁸ Under normal conditions approximately 1/3rd of the circulating platelets are within the spleen. Splenomegaly and hypersplenism results in thrombocytopenia, although the total platelets mass may not be reduced.^{19, 20}

CONCLUSION

It is concluded that significant prolongation of APTT highlights its importance as a reliable marker of coagulopathies in cirrhotic patients. It should be included in the investigation for bleeding tendencies of cirrhotic patients.

REFERENCES

1. Nazish Z, Inayatullah M, Nasir SA, Arshad M, Tanveer S and Naqvi AB. Liver Cirrhosis: clinical presentation. *The professional* 2002; 3: 1- 6.
2. Arif S, Khan AS and Khan AR. Changes in fibrinogen level in liver cirrhosis. *J Ayub Med Coll* 2002; 14:19-21.
3. Kaul W and Munoz S. Coagulopathy of liver disease. *Curr Treat Options Gastroenterol* 2000; 3: 433-38.
4. Mammen EF. Coagulopathies of liver disease. *Clin Lab Med* 1994; 14: 769-80.
5. Scharrer I. Liver Cirrhosis and Coagulopathy. *Hamostaseologic* 2005; 25: 205-8.
6. Wiklund RA. Preoperative preparation of patients with advanced liver disease. *Crit Care Med* 2004; 32: 106-15.
7. Mammen EF. Coagulation abnormalities in liver disease. *Hematol Oncol Clin North Am* 1992; 6: 1247-57.
8. Violi F, Leo R, Vezza E, Basili S, Cordova C and Balsano F. Bleeding time in patients with Cirrhosis: relation with degree of liver failure and clotting abnormalities. *J Hepatol* 1994; 20: 531-6.
9. Glassman AB. Platelet abnormalities in hepatobiliary diseases. National Reference Laboratory, Nashville, TN3 7217.
10. Bernard IM, Palardi G, Pint P, Caletti GC, Brocchi E and Gasbarrini. A study on coagulation profile of patients with cirrhosis of the liver undergoing elective fiberoptic injection sclerotherapy esophageal varices. *Hepato-Gastroenterol* 1984; 31: 125-8.
11. Morag Chisholm. Haematological disorder in liver disease: In sad ar G.H.M. Wright R. Arthur MJP eds. *Wright's liver and biliary disease*. 3rd eds. London W.B. Saunders company 1992; 217.
12. Tomiya T and Fujiwara K. Plasma Thrombin - Anti thrombin III complexes in the diagnosis of primary hepatocellular carcinoma complicating liver cirrhosis. *Cancer* 1991; 67: 481-5.

13. Waterburg L. Haematology for House officers 3rd Eds. Baltimore Williams and Wilkins. 1988; 99-100.
14. Lee S, Yip M and Sachs HJ. Factor IX deficiency in liver disease. Journal of American Medical Association. 1972; 221: 1410-2.
15. Wang M. Studies of P-thromboglobulin thromboxane A2. Prostaglandin 2 concentration and platelet count in liver disease. Zhonghua Net Ke Za Zhi 1992; 31: 80-3.
16. Violi F, Leo R, Vezza E, Basilis S, Cordova C and Balsano F. Bleeding time in patients with cirrhosis: Relation with degree of liver failure and clotting abnormalities. C.A.I.C. Group. J Hepitol 1994; 20: 531-6.
17. Aoki Y, Hirai K and Tanikawa K. Mechanism of thrombocytopenia in liver cirrhosis. Kinetics of indium - II Tropolone Labelled platelets. Eur J Nucl Med 1993; 20: 123-9.
18. Donaldson GWK, Davies SH, Darg A. and Richmond J. Coagulation factors in chronic liver disease. Journal of clinical pathology 1969; 199-204.
19. Aster RH. Pooling of platelets in the spleen: role in the pathogenesis of hypersplenic thrombocytopenia. Journals of clinical investigations 1996: 645-57.
20. Evatt BL, Gibbs WN, Lewis SM and Mc Arthur Jr. Fundamental diagnostic haemtology. The bleeding and clotting disorder 2nd Eds. Atlanta and Geneva. CDC and WHO. 1992; 5.

CORRESPONDENCE ADDRESS:

Dr. Mukamil Shah
Assistant Professor Pathology
Saidu Medical College Saidu Sharif Swat
Cell no. 03439816530.
Email: drmukamilshah@yahoo.com