PROTHROMBIN TIME AS AN INDICATOR OF SEVERITY OF LIVER DISEASES

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ABSTRACT

Objective: *To confirm that Prothrombin time is by and large the most sensitive indicator of hepatocellular function.*

Materials and Method: *Two hundred and twenty patients were recruited in the study from Military Hospital Rawalpindi and combined Military Hospital Peshawar over one year period 1993. All the patient went through a detailed history, hematological and screening tests. The student 't' test was used to assess the significance of results obtained.*

Results: *97% of the patients were males while 69% of the total patients were in the age group of 21-30 years. 93% had viral hepatitis and out of these only 19.50% were Hbs Ag positive. The common symptoms in order of frequency were yellow sclera, loss of appetite, dark urine. Jaundice (97.2%) and palpable liver (81.36) were the most common physical signs. Patients who had PT difference less than 3 seconds from the control had mild hepatitis, while patients who had PT difference more than 3 seconds from the control, had severe hepatitis.*

Conclusion: *PT is a good prognostic indicator of severity of liver diseases and correlates well with the elevation of bilirubin and ALT.*

Key Words: *Prothrombin time, liver disease, indicator.*

INTRODUCTION

The liver plays a central role in the clotting process, and acute and chronic liver diseases are invariably associated with coagulation disorders due to multiple causes.[1] The predominant functions of the liver are the clearance of endo- and xenobiotics, their metabolism and excretion, and the synthesis of biologically important compounds such as clotting factors and albumin.[2] Patients with liver disease often show evidence of defective haemostasis.[3] In chronic liver disease there is not only depression of true prothrombin but also of factor V and factor VII.[4,5]

The term "liver function tests" (LFT) implies standard tests for measurement of synthetic liver function (serum albumins), excretory function (bilirubin) and inflammatory activity of hepatocytes (serum aminotransferases). The utility of these tests in monitoring the immediate liver function is rather low. Likewise, many of these usual laboratory tests other than alanine aminotransferases and bile acids are not specific for hepatic function, and may reflect extrahepatic pathological processes.[6] Coagulation tests have received a lot of attention in view of the fact that they tend to be relatively simple, reliable and easy to perform and may be abnormal when conventional biochemical tests are within normal limits.[7] Therefore these test have proved to be of great practical value in the assessment of acute[8] and chronic liver diseases.[9,10] Among these hematological tests prothrombin time is a universal indicator of liver disease severity.[11]

MATERIAL AND METHODS

Patient inclusion criteria were strict and limited to patients suffering from acute and chronic liver diseases i.e. viral hepatitis, chronic hepatitis and cirrhosis. Therefore some patients who were initially included with a history of an acute haemolytic or obstructive jaundice were excluded from the study.

AGE DISTRIBUTION

Age range	N	%age
1-10	3	1.36
11-20	12	5.45
21-30	151	68.63
31-40	40	18.18
41-50	11	5.00
51-60	3	1.36
Total	220	100

Table 1

In each case a proforma was filled with a detailed history, clinical features and information from the following sets of investigations:

1. Serum Bilirubin (Direct and indirect)

   Serum Alanine Transaminase (ALT)

   Serum Alkaline Phosphatase (ALP)

   Serum Protein

   Serum Albumin

   Serum γ Glutamyl Transferase

To exclude obstructive and haemolytic jaundice and for baseline values a

   Full blood count

   Reticulocyte count

2. Hepatitis viral screen

   HBs Ag

3. Prothrombin Time test

The controls for the prothrombin time test were either healthy volunteers (n=5) for the normal control values and patients on oral anticoagulants (n=5) for the abnormal control values.

Independent 't' test was carried out between two groups i.e. PT difference < 3 seconds and PT difference > 3 seconds considering different liver functions tests. The nature of co-relation was tested among variables of Alanine Transaminase, Alkaline Phosphatase, Protein,Albumin, γ Glutamyl Transferase and Prothrombin Time separately in each group.

RESULTS

Recruitment

A total of 220 patients from Military Hospital Rawalpindi and Combined Military Hospital Peshawar, over a period of one year, where recruited in the study. Out of these 220 patients, 97.28% were male and only 2.72% were female. Male to female ratio being 30.4:1. Disease wise the recruitment is given in Figure-1. 93% were diagnosed viral hepatitis, 4% liver cirrhosis and 3 % were in hepatic coma.

Age wise distribution is given in Table-1. Median age of patients were seen between the age of 21-30 years (68.63%), followed by 31-40 years (18.18%). Mean age of the patients was 28.08 years while the age range varies from 7-60 years.

Presenting symptoms

The presenting symptoms were divided into common and comparatively less common ones. Figure-2 shows that among symptoms yellow sclera (93.16%) anorexia (84.54%) and dark urine (78.18%) were more common than vomiting, fever nausea and abdominal pain. The less common symptoms are given in Figure-3. Among these worth mentioning are burning micturation 3.2% tiredness 2.7% and dizziness 1.8%. Majority of 220 patients had more than one presenting symptom and were therefore classified in more than one category.

Physical signs

The physical signs are shown in figure-4. Jaundice was seen in 97.2% cases followed by palpable liver in 81.36% patients. Only 8.12% patients had both liver and spleen palpable. None of the patients had palpable spleen only. Those patients, who had more than one physical sign, were classified in more than one category.

Laboratory data

In 220 patients 43 were HBsAg positive (19.5%). However serological investigation for

LIVER FUNCTION TESTS

	Range	Mean	S.D
Serum Bilirubin	4-510	147.03 umol/l	81.939
Serum ALT	19-1651	657.38 u/l	357.773
Serum ALP	113-1861	389.04 u/l	199.53
Serum ? GT	25-316	130.12 u/l	74.72
Serum Protein	4-79	65.85 g/l	4.3717
Serum Albumin	20-49	36.54 g/l	5.503

Table 2

PROTHROMBIN TIME

	Group-A PT difference<3 sec			Group-B PT difference>3 sec				
	N	Mean	S.D	N	Mean	S.D	t. cal	P value
Age	152	28	7.28	68	28.26	7.29	0.2445	N.S
PT Diff	152	1.76	1.041	68	8.41	15.46	3.594	<0.01
Bilirubin	152	123.88	70.545	68	198.73	84.96	6.3496	<0.01
ALT	152	555.3	315.20	68	885.52	345.67	6.725	<0.01
ALP	152	374.08	222.66	68	422.47	128.78	2.0267	<0.05
? GT	40	118.15	66.148	24	150.08	78.91	1.6693	N.S
Albumin	42	37.5	5.41	22	34.727	4.548	21.673	<0.05
Protein	53	66.26	4.49	23	64.91	4.02	1.2972	N.S

Table 3

other viral hepatitis markers i.e HAV, HCV, HEV were not done. Liver Function Tests were deranged in all cases. Excessively raised Serum Bilirubin, serum Alanine Transaminase (ALT), serum Alkaline phosphatase and serum γ Glutamy Transferase were encountered in all the patients while the levels of serum Protein and serum Albumin were normal in all cases of viral hepatitis but were low in cases of liver cirrhosis. The minimum and maximum. ranges found in this study along with Mean and Standard Deviation of liver function tests are given in Table -2.

Prothrombin time

Three seconds were taken as a cutoff value in the prolongation of prothrombin time (PT) from control value. Based on this prolongation of PT, the patients were divided into two groups i.e group A with less than 3 seconds PT difference and group B with more than 3 seconds PT difference as shown in Table-3. 152 patients (69%), whose prothrombin time difference was less than 3 seconds fall in Table-3 group A, while 68 patients (31%) whose prothrombin time difference

PEARSON CORELATION CO-EFFICIENT

Variables	PT Difference < 3	PT Difference > 3
Age	-0.0391	-0.1726
	0.6308	0.1625
	153	67
Bilirubin	0.1929 significant at P<0.05	0.4946 significant at P<0.01
	0.0169	0.0001
	153	67
ALT	0.1838 significant at P<0.05	0.3413 significant at P<0.01
	0.0197	0.0047
	153	67
ALP	0.01907	0.07135
	0.8150	0.5661
	153	67
γ GT	0.12244	0.05263
	0.9398	0.8208
	42	21
Protein	-0.08310	0.18335
	0.5351	0.4024
	58	23
Albumin	-0.15629	-0.1334
	0.3169	0.5645
	43	21

Table 4

RECRUITMENT-DISEASE WISE

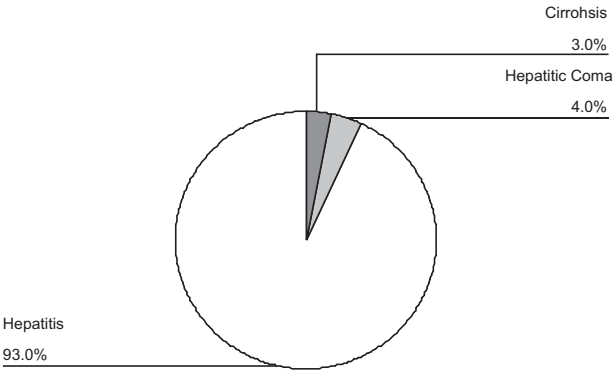

Figure-1

COMMON PRESENTING SYMPTOMS

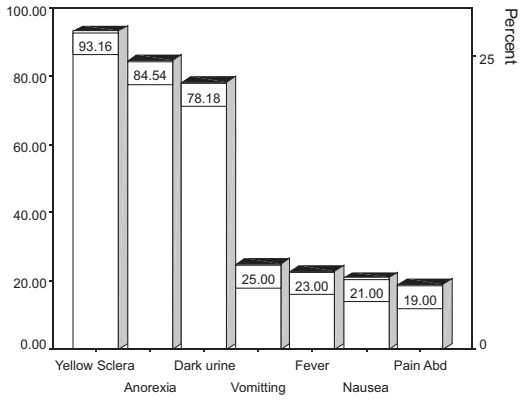

Figure-2

was more than 3 seconds fall in Table-3 group B. The mean age in both groups was 28 years and the difference was not significant (P value not significant). Serum γ Glutamyle Transferase and Serum Protein in the two groups were also not significant. Serum Albumin was significant (P<0,05). Where as Serum Alkaline Phosphatase was significant at P<0.05 but was not found significant at P=0.01. While Serum Bilirubin, Serum Alanine Transaminase and Prothrombin Time were highly significant (P<0.01).

Analysis of co-efficient of co-relation.

The purpose of this analysis was to see if any individual biochemical functions lay concealed with in the six liver function tests.

PT-Difference <3

As far as correlation of PT in normal cases is concerned we found that it has significant correlation with variable of Bilirubin and ALT. However the Significance is at P-value of 0.05 and not at 0.01.

Further it is noted that Prothrombin has negative correlations with variables of Age, PT and Albumin individually, however these correlation are found to be not significant. Similarly PT has weak positive correlations with ALP and γ GT.

PT-Difference >3

In the observed cases where PT-D >3, prothrombin time seems to be strongly correlated with BilirubinILI and the positive correlation is significant even at P< 0.01. The same is the case of PT with ALT which has significant correlation. Here again PT is negatively correlated with Age and Albumin individually but these correlation are not significant. Similarly as was the situation in the normal cases, here again PT has weak positive correlations with ALP and GGT which are not significant.

LESS COMMON PRESENTING SYMPTOMS

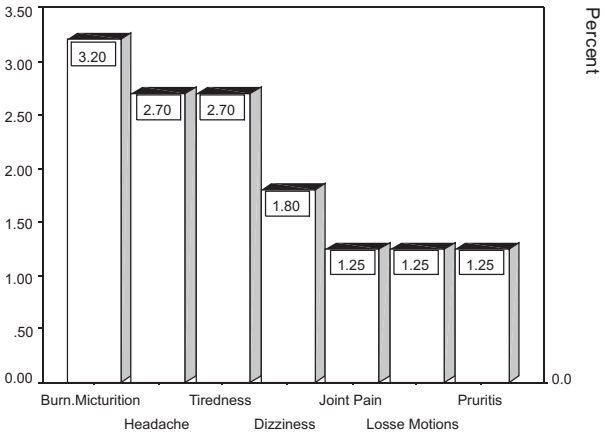

Figure-3

PHYSICAL SIGNS

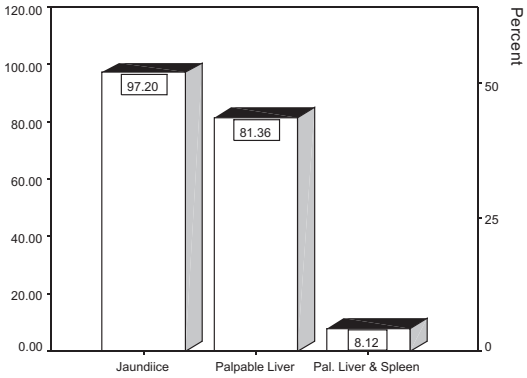

Figure-4

Comparing the correlation co-efficient of Prothrombin Time with the rest of the variable in PT < 3 Sec with the corresponding co-efficient in PT > 3 Sec, it is noted that the correlation found for PT-D>3 Sec are greater as compared to their counterpart in PT-D < 3 Sec, except for the variables γ GT and Albumin.

Overall the co-efficient correlation analysis revealed with Prothrombin Time has significant positive correlation with variable of Bilirubin and ALT as shown in Table-4.

DISCUSSION

Hepatitis was the most common liver disorder in this study. Of the 205 hepatitis cases, 43 (19.50%) were Hbs Ag positive. The remaining 176 cases were not screened for any other viral markers. In the similar studies,[12,13] the incidence of hepatitis B has been shown as 45% and 23% respectively.

About 75% of the cases studied, were upto the age of 30 years, with the male preponderance. It was interesting to note that the frequency of liver disease decreased with the increasing age after 30 years.

The clinical presentation of our cases indicates that most patients presented with yellow sclera, loss of appetite followed by dark urine. Vomiting, fever, nausea and abdominal pain were comparatively less frequent. Clinical examination revealed jaundice and hepatomegaly in majority of these cases. The clinical presentation of our study is consisted with the similar study.[14]

Prothrombin time has a high prognostic value in acute liver disease and is a much better index than the bilirubin, transaminase or albumin.[15] Similarly in our study, prothrombin time was of better prognostic value. This is evident from Table-3, where in group A, the patients with mild hepatitits had normal prothrombin time while their bilirubin and transaminase were raised. Also on con-efficient co-relation analysis, the prothrombin time in group A has sufficient correlation with bilirubin and transaminase but this significance is at P value of 0.05 and not at 0,01. On the other hand, in group B, patients with severe hepatitits, the prothrombin time was prolonged along with significantly raised bilirubin and transaminase. Similarly on co-efficient co-relation analysis, the prothrombin time in group B is strongly correlated with bilirubin and transaminase and the positive correlation is even significant at P<0.01. It was interesting to note that in both groups, the serum protein value was normal.

Quick one stage test as the most reliable single test for assessing deficiency of plasma coagulation factors and a markedly prolonged prothrombin time to twice its normal level is a poor prognostic sign.[16] This fact was also true in our study. There were six patients with hepatic coma in our study. Out of these six patients, five had prothrombin time twice its normal level, and all of them died. While one patient who had normal prothrmbin time, recovered.

Prothrombin ratio was the best prognostic index in acute hepatic failure.[17] Similarly in acute hepatitis Normotest and thrombotest returned to normal before most other biochemical tests indicating good synthetic function of the liver cells. Serum bilirubin and aspirate transaminase were the last to return to normal.[18] Our study also confirms this finding.

Prolongation of the Prothrombin time is associated with widespread defects of the vitamin K dependent factors and factor V and the degee of prolongation of the Prothrombin time is an indication of their severity.[19] Dymock[20] found that the level of factor VII was a useful guide to recovery in acute failure and suggested that it should be specifically measured. Losowsky[21] thought that coagulation measurements had little prognostic value in liver disease with the exception of Prothrombin time in acute hepatic necrosis. Owren[22] and Biland[23] have regarded a fall in factor V as an important indicator of failing liver function although the later found factor XIII and plasminogen of greater prognostic significance.

Mannucci[24] found prothrombin to be decreased in patients with acute hepatitis when assayed. Serum bilirubin and transaminase were not correlated with either prothrombin or anti thrombin, on the contrary a significant correlation could be established between prothrombin, serum albumin and pseudocholinesterase. While in our study, in severe hepatitis, Prothrombin time correlated significantly with serum bilirubin and transaminase.

Prothrombin and factor VII (P&P test) was found to be valuable in liver cirrhosis[25] Riuz et al[26] analysis confirms the Prothrombin time test as the single most useful clotting test of hepatic function. Albumin, factor II and X fall together when protein synthesis deteriorates. The inverse association between aspartate aminotranferase and factor IX could be explained by leakage of enzymes into the blood with liver cell damage. The positive correlation between bilirubin and VIII c and between aspartate aminotransferease and factor V are not surprising since both factors participate in acute phase reaction.[27, 28]

Mosher[29] reported that a poor prognosis is associated with prolonged prothromin time by more than 4-5 seconds that does not respond to parenteral Vitamin K therapy.

Patrassi et al[30] concluded that prothrombin time and factor VII actively were more sensitive than protein C activity as an early prognostic indices of clinical outcome in orthotopic liver transplantation. Scheig[31] concluded that prothrombin time and serum albumin level are excellent gauges of hepatic protein synthetic ability, where as the bilirubin level is probably the best test of overall function. The transaminase levels give a day by day account of the amount of hepatocellular injury.

CONCLUSION

Hepatitis is the commonest disorder among the liver diseases. Males between the ages 21-30 years were mainly affected. Most of the patients presented with yellow sclera, loss of appetite and dark urine. Jaundice and hepatomegaly were the main physical signs. Only 19.50% of the total patients were HBsAg positive. All the patients had elevated bilirubin, ALT which correlated significantly with PT. On over all analysis the co-efficient of correlation revealed that prothrombin time has significant positive correlation with variables of bilirubin and ALT.

REFERENCES

1. Lucio A, Guardascione, Maria A, Brancaccio, Vincenzo et al. Coagulation Disorders in Liver Disease. Seminars in Liver Disease. 2002;22(1):83-96
2. Tygstrup N. Assessment of liver function: principes and practice. J Gastroenterohe-patology 1990;5:468-82.
3. Deutsch E. Blood coagulation changes in liver diseases. Progress in liver disease (Ed by H Popper and F Schaffner) Grune & Stratton New York. 1965;2:69
4. Owren PA. The diagnostic and prognostic significance of plasma prothrombin and Factor V in parenchymatous liver disease and obstructive jaundice. Scand J Clin Lab Invest. 1949 ; 1:131-140.
5. Stefanini M. Haemorrhagic diathesis of liver dysfunction and obstructive jaundice. Proc 3rd International Congress. Internet Soc Haemat. 1951;84
6. Morgan DJ, Elliott SL, Ghabrial H. Quantitative liver function test: a realizable goal?. Can J Gastroentrol 1991; 5, 77-85.
7. Poller L. Coagulation abnormalities in liver disease in Recent Advances in Blood Coagulation. Churchill Livingstone, Edinburgh London & New York. 1977:267-292
8. Gallus AS, Lucas CR, Hirsh J. Coagulation studies in patients with acute infectious hepatitis. Bri J Haematol.1972;22: 761-771
9. Specter I, Corn M. Laboratory tests of haeomstasis. The relation to haemorrhage in liver disease. Archives of internal medicine. 1967; 119: 577-582
10. Donaldson GWK, Davies SH, Darg A, Richmond J. Coagulation factors in chronic liver disease. J Clin Path. 1969;22:199-204
11. Robert A, Chazouillères O. Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio? Hepatology. 1996 ;24(6):1392-4.
12. Zuberi SJ, Lodi TZ, Alam SE. Spectrum of viral hepatitis. JPMA 1991;41:288.
13. Malik IA, Anwar CM, Luqman M. The pattern of acute viral hepatitis in children: a case study based on seroe-pidemiology and biochemical profile. JPMA 1987; 37:314-317
14. Ahmad M, Quraishi MS, Mushtaq S et al. Acute sporadic hepatitis non A non B, Clinical features and biochemical profile. JPMA. 1989;39:307-309
15. Corrigan JJ. Diagnosis and therapy of coagulopathies in patients with liver disease. Contemp Anesth Pract. 1981;4:1-11
16. Cwling DC. Coagulation defects in liver disease. J Clin Path. 1956; 9: 347.
17. Cook GC, Sherlock S. Jaundice and its relation to therapeutic agents. The Lancet. 1965. 175-179
18. Hillenbrand P, Sherlock S. Use of Nortest and thrombotest coagulation tests in hepatocellular diseases. Scand J Gastroent.1974;Suppl 19:125-131
19. Riuz F, Grainger S, Hall RJC, Ingram GIC, Pollard V, Swan AV. Relation of simple clotting tests to clotting factor levels in liver disease. Clin lab Haemat. 1982;4:247-256.
20. Dymock IW, Tucker JS, Woolf IL. Coagulation studies as a prognostic index in acute liver failure. Br J Haematol.1975;29:385-95
21. Losowsky MS. Impaired coagulation in the bleeding of chronic liver disease.J Roy Coll Phycns.1973; 8(1): 79-86
22. Owren PA. The diagnosis and prognostic significance of plasma prothrombin and factor V in parenchymatous liver disease and

obstructive jaundice. Scand J Clin Lab Invest. 1949; 1:131-140

23 Biland L, Duckert F, Prisender S, Nyman D. Quantitative estimation of coagulation factors in liver disease. Thromb Haemostas. 1978. 39;646-56.

24. Mannucci PM. Estimation of prothrombin in liver disease. J Cli Path.1970; 23:291-295

25. Hallen A and Nilson IM. Coagulation studies in liver disease: Thromb Diathes Haemorrh 1964; 11:51-63.

26 Riuz F, Grainger SL,Hall RJC, Ingram GIC, Pollard V & Swan AV. Relation of simple clotting tests to clotting factor levels in liver disease. Clin Lab Haemat. 1982;4:247-256.

27 Egeberg O. Anti haemophilic A factor (factor VIII) and fibrinogen in human blood. Scand J clin lab Invest 1962; 14,230.

28 Brozovic M, Physiological mechanism in coagulation andfibrinolysis.Br med Bull. 1977; 33:231.

29. Mosher DF.Disorders of blood coagulation. Wyngaarden JB, Smith LH (ends). Cecil's textbook of medicine 18th edition. Philadelphia. WB Saunders Co. 1988:1060.

30. Patrassi GM, Sartori MT, Viero M et al. Protein C,factor VII and prothrombin time as early markers of liver function recovery or failure after liver transplantation. Blood Coagul fibrinolysis 1993; 1: 131-140.

31. Scheig R.Evaluation of tests used to screen patients with liver disorders. Prim Care 1966;23(3):551-60.

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