PROSPECTIVE COHORT COMPARING CLINICAL FEATURES AND LABORATORY PARAMETERS BETWEEN ACUTE AND CHRONIC HEPATITIS

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ABSTRACT

BACKGROUND

India has a high prevalence of hepatitis B. The present study was undertaken to understand the clinical, biochemical and virological characteristics of HBV infected patients and also to describe the natural course of the disease and the progression to chronic infection.

MATERIALS AND METHODS

Our prospective cohort study enrolled 100 patients with HBV infection presenting to Government Medical College, Trivandrum for 6 months. Participants with previous history of chronic liver disease, jaundice, and severe systemic disease were excluded. Institutional ethics committee approved the study and written informed consent was obtained from all participants. Data included socio-demographic parameters, history and laboratory investigations (baseline, 1 month & 6 months of enrolment). Laboratory investigations were done in the central laboratory of the institution. Participants with positive HBsAg after 6 months of treatment were considered as chronic hepatitis. Data was analysed using free software R®, independent sample 't' test, paired t-test and repeated measures ANOVA were used as tests of significance and $p<0.05$ was considered significant.

RESULTS

HBV infection was more prevalent among males. Icterus was associated with positive anti-HBcIgM ($p=0.01$) and HBeAg ($p=0.04$). Significant association was observed between positive HBeAg and splenomegaly ($p=0.03$). Hepatomegaly ($p<0.001$), US evidence of liver disease ($p<0.001$) and chronic hepatitis was associated. Transaminases, bilirubin, and INR showed reduction over 6 months of treatment with improvement in albumin levels. Between acute and chronic hepatitis, the change in transaminase, serum albumin & INR was significantly different.

CONCLUSION

Chronic hepatitis treatment results in a higher reduction of transaminases, albumin, and INR compared to acute hepatitis.

KEYWORDS

Chronic Hepatitis, HBeAg, Anti-HBcIgM, AST, ALT.

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BACKGROUND

Hepatitis B virus (HBV) is a DNA virus with an RNA intermediate which integrates into the host genome and causes persistent infection. 240-350 million people worldwide are chronically infected with HBV[1,2] and has contributed to 887, 000 deaths in 2015.[3] India is home to 10-15% of global HBV carriers and the prevalence of HBV ranges between 2-8% and 15.9% among tribal population.[4-6] The true burden and prevalence of the disease remain elusive due to the voluntary nature of the participants enrolled in prevalence studies.

The major mode of HBV transmission is by exposure to infected blood, semen, and vaginal secretions. Though HBV has been detected in other body fluids, the transmission of disease via these fluids is minimal.[7] The risk of HBV infection is high due to the increased survival of the virus outside the host for a longer durations compared to other infective virus.[8] Except the impoverished, global healthcare related transmission of HBV has declined[9] over the past few decades due to the implementation of stringent transmission control measures. HBV is transmitted perinatally in high prevalence regions, perinatally or horizontally in intermediate prevalence regions and via sexual contact, intravenous drug abuse, infected blood, and blood products in low prevalence regions. The spectrum of HBV infection ranges from asymptomatic infections (66%) to cirrhosis, acute liver failure (1%)[10] and hepatocellular carcinoma (HCC)[11] with an estimated 5-year survival rate of 50%[12,13] in chronic infections. Laboratory abnormalities observed in HBV infections are in serum bilirubin, aspartate aminotransferase

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(AST), alanine aminotransferase (ALT), prothrombin time (PT), serum albumin and platelet count. High infectivity, lack of complete cure of HBV and India being the second largest population of the world necessitates research on the topic. The present study was undertaken to understand the clinical, biochemical and virological characteristics of HBV infection and to describe the natural course of the disease and the progression to chronic infection.

MATERIALS AND METHODS

Our prospective cohort study enrolled 100 participants with HBV infection (clinical features of viral hepatitis and positive hepatitis B surface antigen (HBsAg)) admitted under General Medicine and Medical Gastroenterology department of Government Medical College Trivandrum during a period of 6 months. Participants with previous history of chronic liver disease, jaundice and severe systemic disease were excluded. Institutional ethics committee approved the study and written informed consent was obtained from all participants. Sample size was calculated assuming α of 0.05, β of 0.2, prevalence of 1-10% with a maximum prevalence of 14% and a 10% attrition rate. Data was collected in semi-structured case record forms which included socio-demographic parameters (age, gender), history (prior admission, blood transfusion, vaccination, dental procedures, high-risk sexual practices) and laboratory investigations (HBsAg, hepatitis B e antigen (HBeAg), IgM antibodies against hepatitis B core antigen (anti-HBcIgM), AST, ALT, total bilirubin (T. bil) and International normalized ratio (INR)). All participants were followed up for a period of 6 months and the investigations were repeated after 1 month (1st follow up) and 6 months (2nd follow up) of enrolment. All investigations were done in the central laboratory of the in situation using appropriately standardized techniques and B-mode ultrasonography (US) was used to evaluate the liver. Participants with positive HBsAg after 6 months of treatment were categorized as chronic hepatitis. Data were analyzed using free software R® and are expressed as mean (standard deviation (SD)), median (interquartile range (IQR)) and as frequency. Participants were categorized based on the type of hepatitis (acute and chronic), HBeAg and anti-HBcIgM positivity. Independent sample 't' test, paired 't' test and repeated measures ANOVA were used as tests of significance and a $p<0.05$ was considered significant.

RESULTS

79% (n=79) participants were males and 21% (n=21) were females. Baseline parameters of the study participants are demonstrated in table 1. Maximum proportions of participants were in age groups 20-39 years and 40-59 years (Table 2). 22% (n=22), 48% (n=48), 15% (n=15), 23% (n=23) and 80% (n=80) participants had history of surgery, hospital admission, blood transfusion, alcohol consumption, and dental procedures respectively. 85% (n=85), 14% (n=14) and 31% (n=31) participants had icterus, hepatomegaly and splenomegaly respectively. Positive HBeAg and anti-HBcIgM were seen in 69% (n=69) and 91% (n=91) participants respectively. 7% (n=7) participants had US evidence of chronic liver disease.

Parameter	n	Mean (SD), Median (IQR)
Age (Years)	100	42.6 (16.2), 43 (28.3-55.5)
ALT (IU/L)	100	1022.3 (825.3), 1007.5 (192.8-1451)
AST (IU/L)	100	888.6 (909.9), 800 (184.5-1139.8)
T. Bil (mg/dl)	100	11.1 (7.3), 11.5 (4.5-16)
Serum Albumin (mg/dl)	100	3.9 (0.5), 4 (3.6-4.2)
INR	100	1.3 (0.3), 1.2 (1.1-1.4)

Table 1. Baseline Parameters of Study Participants

Age (Years)	n (%)
< 20	6 (6)
20 - 39	38 (38)
40 - 59	38 (38)
60 - 79	18 (18)

Table 2. Age Distribution of Study Participants

Among participants with acute hepatitis, 45.2% (n=42), 12.9% (n=12), 20.4% (n=19) and 22.6% (n=21) had history of hospital admission, surgery, blood transfusion and alcohol consumption respectively. 85.7% (n=6), 42.9% (n=3), 42.9% (n=3) and 28.6% (n=2) participants with chronic HBV infection, gave a history hospital admission, prior surgery, blood transfusion and alcohol consumption respectively. All chronic HBV participants were icteric. Distribution of AST and ALT among study participants are demonstrated in table 3 and 4 respectively.

AST (IU/L)	Baseline (n)	1st Follow-Up (n)	2nd Follow-Up (n)
20 - 40	0	0	19
40 - 120	11	33	74
120 - 200	19	16	2
≥ 200	70	51	5

Table 3. Stratified Frequency Table Demonstrating the Distribution of AST

ALT (IU/L)	Baseline (n)	1st Follow-Up (n)	2nd Follow-Up (n)
20 - 40	0	1	16
40 - 120	5	31	78
120 - 200	20	15	2
≥ 200	75	53	4

Table 4. Stratified Frequency Table Demonstrating the Distribution of ALT

Participants with positive HBeAg had significantly higher mean AST (1017.2 (934.8) vs. 602.4 (793.1), $p=0.03$), T. bil (13.3 (7.3) vs. 6.3 (4.4), $p<0.001$) and INR

(1.3 (0.3) vs. 1.2 (0.3), p=0.02) at baseline, T. bil (6.8 (4.6) vs. 3.4 (2.4), p<0.001) and INR (1.2 (0.2) vs. 1.1 (0.2), p=0.009) at 1st follow-up and INR (1.1 (0.1) vs. 1 (0.1), p=0.01) at second follow-up. HBeAg positive participants had significantly higher reduction in AST from baseline to 1st follow-up (632.7 (725.6) vs. 340.3 (518.2), p=0.04). Anti-HBcIgM positive participants had significantly higher ALT (359.8 (343.9) vs. 132.4 (126.2), p<0.001) and AST (368.5 (386.7) vs. 125.1 (161.2), p=0.002) at 1st follow-up and had significantly higher reduction in ALT (300.9 (329.2) vs. 92.1 (123.3), p=0.001) and AST (301.3 (345.4) vs. 79.9 (158.5), p=0.003) from 1st to 2nd follow-up. No association with positive HBeAg was observed for gender (p=0.6), prior surgery (p=0.9), prior hospital admission (p=0.2), prior blood transfusion (p=0.7), alcohol consumption (p=0.3) and hepatomegaly (p=0.7). No association with anti-HBcIgM positivity was observed for gender (p=0.1), prior surgery (p=0.4), prior hospital admission (p=0.4), prior blood transfusion (p=0.2), alcohol consumption (p=0.4), hepatomegaly (p=0.7) and splenomegaly (p=0.2). Icterus was associated with positive anti-HBcIgM (p=0.01; OR: 5.8, 95% CI 1.4-25) and HBeAg (p=0.04, OR: 3.1, 95% CI 1-9.5). Significant association was observed between positive HBeAg and splenomegaly (p=0.03; OR: 3.1, 95% CI 1.1-9.2).

No association with chronic hepatitis was observed for gender (p=0.6), prior surgery (p=0.2), prior hospital admission (p=0.05), prior blood transfusion (p=0.07), alcoholism (p=0.7), icterus (p=0.6), splenomegaly (p=0.3), HBeAg positivity (p=0.3) and anti-HBcIgM positivity (p=0.4). Significant association with chronic hepatitis was observed for hepatomegaly (p<0.001; OR: 63.8, 95% CI 6.8-597.4) (table 5) and US evidence of liver disease (p<0.001). Comparison of baseline parameters showed a significant reduction in all parameters over 1st follow-up and 2nd follow-up except serum albumin (table 6). Significantly higher reduction of AST, ALT and serum albumin was observed in the first month of treatment (table 7).

Hepatomegaly	Hepatitis B		Total
	Chronic	Acute	
Yes	6	8	14
No	1	85	86
Total	7	93	100

Table 5. Association between Hepatomegaly and Type of Hepatitis

A significant association was observed between hepatomegaly and type of hepatitis (p<0.001; OR: 63.8; 95% CI 6.8-597.4) indicating a 63.8 Odds of encountering chronic hepatitis in participants with hepatomegaly.

Parameter	Baseline Mean (SD), Median (IQR)	1st follow-up Mean (SD), Median (IQR)	2nd follow-up Mean (SD), Median (IQR)	P
AST (IU/L)	881.6 (909.6), 800 (184.5-1139.8)	346.6 (378.1), 209 (83-505.3)	65.2 (86.7), 43.5 (40-53)	<0.001*
ALT (IU/L)	1022.3 (825.3), 1007.5 (192-1451)	339.3 (336.3), 219.5 (98-452.3)	42.6 (16.2), 45 (52-56)	<0.001*
T. Bil (mg/dl)	11.1 (7.3), 11.5 (4.5-16)	5.7 (4.4), 5 (2-7.9)	1.5 (0.6), 1.4 (1.2-1.7)	<0.001*
Serum albumin (mg/dl)	3.9 (0.5), 4 (3.6-4.2)	3.9 (0.5), 4 (3.4-4.2)	4 (0.4), 4 (3.8-4.2)	0.003∫
INR	1.3 (0.3), 1.2 (1.1-1.4)	1.1 (0.2), 1.1 (1-1.2)	1.1 (0.1), 1 (1-1.1)	<0.001*

Table 6. Parameters at Enrolment, 1st and 2nd Follow up

*indicates a significant difference in parameters between baseline, 1st, and 2nd follow-up, ∫ indicates significant a difference in parameter between 1st and 2nd follow-up (repeated measures ANOVA).

Parameter	N	Mean Change during 1st Follow-Up (SD)	Mean Change from 1st to 2nd Follow-Up (SD)	P
ALT (IU/L)	10	683 (663.3)	282.1 (321.5)	0.02*
AST (IU/L)	100	542.1 (679.3)	281.4 (338.4)	<0.001*
T. Bil (mg/dl)	100	5.4 (5)	4.3 (4.2)	0.06
Serum Albumin (mg/dl)	100	0.04 (0.3)	-0.1 (0.3)	<0.001*
INR	100	0.1 (0.2)	0.1 (0.1)	0.5

Table 7. Change in Baseline Parameters

*indicates significant difference between groups using paired t-test.

Significantly higher ALT and AST was observed through-out the study period in participants with chronic hepatitis. Participants with chronic hepatitis had significantly higher T. bil (at 1st and 2nd follow-up) and INR (baseline) (Table 8).

Participants with chronic hepatitis had a higher reduction in ALT throughout the study period. Reduction of the study parameters is demonstrated in table 9.

Parameter	Type of Hepatitis	N	Baseline Mean (SD)	p	1st Follow-Up Mean (SD)	p	2nd Follow-Up Mean (SD)	p
ALT (IU/L)	Chronic	7	2456.7 (939.4)	<0.001*	712.1 (497.4)	0.002*	182.4 (65.1)	<0.001*
	Acute	93	914.3 (712.1)		311.3 (306.9)		47.8 (11.3)	
AST (IU/L)	Chronic	7	1601.7 (1160.6)	0.03*	838.9 (453.5)	<0.001*	244.7 (208.4)	<0.001*
	Acute	93	834.9 (872.6)		309.5 (347.2)		51.7 (51.3)	
T.bil (mg/dl)	Chronic	7	14.2 (8.9)	0.3	9.2 (4.8)	0.03*	2.6 (1.1)	<0.001*
	Acute	93	10.9 (7.2)		5.5 (4.3)		1.4 (0.4)	
Serum Albumin (mg/dl)	Chronic	7	4.2 (0.4)	0.1	4 (0.4)	0.6	3.9 (0.5)	0.5
	Acute	93	3.9 (0.5)		3.9 (0.5)		4 (0.3)	
INR	Chronic	7	1.7 (0.2)	<0.001*	1.2 (0.07)	0.4	1.1 (0.1)	0.3
	Acute	93	1.3 (0.2)		1.1 (0.2)		1.1 (0.1)	

Table 8. Comparison of Parameters between Acute and Chronic Hepatitis

*indicates significant difference between groups using independent sample t-test.

Parameter	Type of Hepatitis	N	Mean Change During 1st Follow-Up (SD)	P	Mean Change from 1st to 2nd Follow-Up (SD)	p	Mean Change from Baseline (SD)	P
ALT (IU/L)	Chronic	7	1744.6 (1174.7)	<0.001*	529.7 (477)	0.03*	2274.3 (905.3)	<0.001*
	Acute	93	603.1 (539.6)		263.5 (302.3)		866.5 (706.6)	
AST (IU/L)	Chronic	7	762.9 (898.7)	0.3	594.1 (300.5)	0.01*	2212 (843)	<0.001*
	Acute	93	525.4 (663.2)		257.8 (330.7)		862.7 (706.5)	
T.bil (mg/dl)	Chronic	7	5 (9.1)	0.8	6.6 (4.5)	0.1	11.6 (8.5)	0.5
	Acute	93	5.4 (4.7)		4.1 (4.2)		9.5 (7.1)	
Serum Albumin (mg/dl)	Chronic	7	0.2 (0.2)	0.2	0.06 (0.1)	0.1	0.3 (0.2)	<0.006*
	Acute	93	0.03 (0.3)		-0.1 (0.3)		-0.1 (0.3)	
INR	Chronic	7	0.6 (0.2)	<0.001*	0.1 (0.2)	0.8	0.6 (0.3)	<0.001*
	Acute	93	0.1 (0.2)		0.06 (0.1)		0.2 (0.2)	

Table 9. Change in Study Parameters between Acute and Chronic Hepatitis

*indicates significant difference between groups using independent sample t-test.

DISCUSSION

A higher proportion of male participants (79%) enrolled in our study indicating the higher risk of contracting HBV among males. This is attributable to high-risk behavior and accidental exposure among males at hair salon,s,[14] tattoo parlours,[15] and dental clinics[16] and could also be due to the expression of a variant of estrogen receptor in males which cause rapid progression of disease and development of cirrhosis and HCC.[17] The mean age of the study participants was 42 years, and the maximum proportion of participants were in the age group between 20-60 years which is comparable to published literature suggesting highest incidence in the age range of 16-50 years.[18] The exact reason for the higher prevalence of HBV in these age groups has not been clearly described, although it could indicate contraction of disease early in life[19] and reduced longevity[12] among HBV infected individuals. Hospital admissions,[20] dental procedures,[21] blood transfusion[20] and surgeries[22] are described as risk factors of hepatitis B infection and 48%, 80%, 15% and 22% participants respectively reported a history of these risk factors. Alcoholic liver damage accelerate the progression of HBV infections[23] and a positive history was present in 23% participants. Predominant number of participants were symptomatic in contrast to previous reports of two thirds of acute hepatitis being asymptomatic.[24] Being a tertiary care facility, higher proportion of those seeking medical attention in our institution would be for their symptom which also explains the 85%, 14% and 31% participants with jaundice, hepatomegaly, and splenomegaly respectively. HBeAg is a marker of HBV replication[25] and was seen in 69% of participants and anti-HBcIgM was seen in 91% participants and has been considered a valuable tool in differentiating acute and chronic HBV infection.[26] 16% and 7% participants had sonological evidence of liver disease and chronic liver disease respectively. A coarse pattern of the liver has been described as a common finding in acute hepatitis.[27] Cirrhotic pattern has been described in 2.1-6% participants[28] which could be due to the absence of symptoms in some patients leading to progression and cirrhosis.[24]

Hospital admissions have been described as a risk factor for hepatitis B infection[29,30] and was present in 45% and 85% of acute and chronic hepatitis patients respectively. 82% and 100% participants with acute and chronic hepatitis

respectively had icterus which is considered a major symptom[31] due to hepatocyte involvement and has been described in 76% HBV infections.[32] Typically an anicteric phase followed by icteric phase is seen.[31] Mean AST, ALT and serum bilirubin among the participants were higher than normal limits. Elevation of hepatic transaminases is due to the cell-mediated immune response resulting in hepatocyte apoptosis and necrosis.[33] Elevated serum bilirubin is considered as a symptom of advanced cirrhotic disease,[34] which indicates enrolment of a higher number of participants with advanced hepatic disease in our study probably due to the absence of symptoms of hepatitis B. Significantly higher INR could be due to the reduction in synthesis of clotting factors by liver due to hepatocyte involvement.[35]

Participants with positive HBeAg were having significantly higher AST (baseline), total bilirubin (baseline and 1st follow up) and INR (baseline, 1st and 2nd follow up). The reasons for this finding cannot be explained on the basis of present literature since HBeAg negative HBV infections are described as infections caused by a variant HBV.[36] Anti-HBcIgM positive participants had significantly higher transaminases at 1st follow up. Icterus was associated with positive HBeAg and anti-HBcIgM; this could indicate the severity of hepatocyte damage in these participants. Splenomegaly was associated with positive HBeAg which has been previously described.[37] Males[38] are described as at higher odds of developing chronic HBV infection[18] our study did not demonstrate any such association. The higher awareness among female participants could lead to enrolment of higher number of females. No association of surgeries, blood transfusion and hospital admission with chronic HBV infection was observed though they are described as risk factors of chronic HBV infection.[29] The exemplary health care policies of the state government might have contributed to this by reduced HBV transmission through surgeries, hospital admissions and blood transfusion. Association of alcoholism, icterus, splenomegaly, positive HBeAg and anti-HBcIgM with chronic HBV infection was not observed. Since alcohol consumption accelerates the progression of liver disease,[23] observation from our study is perplexing. Icterus being a symptom of majority of HBV infection[31] explains our observation. Splenomegaly and its association with severe hepatitis, cirrhosis and HCC[24] has been described. Our finding could probably be due to the small sample size or due to the high prevalence of febrile illness causing splenomegaly (leptospirosis and dengue fever) in our setting.[39,40] No association with chronic hepatitis was observed for anti-HBcIgM and HBeAg, though these parameters have been described as predictors of severity. Significant association between hepatomegaly and chronic hepatitis was observed similar to previous reports and HBV has even been described as a cause for fulminant life threatening hepatitis.[32]

AST, ALT, total bilirubin, serum albumin and INR showed significant change over 6 months probably indicating the effectiveness of antiviral therapy. Antiviral treatment reduce hepatocyte damage causing reduction in AST,[41] ALT,[41] total bilirubin,[42] INR[43] and cause increase in albumin production.[44] Significantly higher reduction in AST and ALT was observed in the first month of treatment which is due to the improvement in liver function. Serum albumin reduced in the initial month of treatment and subsequently increased over 6 months, since the synthetic functions of liver take longer time to revert to normalcy,[44] Participants with chronic hepatitis had significantly higher AST and ALT throughout the study period. Chronic hepatitis, due to persistent insults to the hepatocytes such as interferon-β induced apoptosis, necrosis and degeneration[45] leads to elevation in transaminases.[46] Participants with chronic hepatitis had significantly higher serum bilirubin at follow-ups possibly due to the higher reduction of serum bilirubin in acute hepatitis with treatment. Chronic hepatitis patients due to the higher impairment of synthetic functions of liver[44] had significantly higher INR at baseline. Participants with chronic hepatitis had higher reduction in ALT throughout the entire study period which could be due to improvement in cholestasis of chronic hepatitis patients with antiviral treatment.[47] AST reduction was higher at 6 months for participants with chronic hepatitis due to improvement in hepatocyte integrity[47] following antiviral therapy. Significantly higher reduction in serum albumin was observed in participants with chronic hepatitis at 6 months where as an overall increase in serum albumin was observed in participants with acute hepatitis. This indicates the improvement in synthetic functions of liver in acute hepatitis. Significantly higher reduction in INR was observed at 1st follow up in participants with chronic hepatitis due to an improvement in synthetic functions of the liver with antiviral treatment.

CONCLUSION

In our study males were found to be predominantly infected with HBsAg. Significant association of hepatomegaly and US evidence of liver disease was seen with chronic hepatitis. Transaminases, bilirubin and INR showed significant reduction over 6 months of treatment and albumin showed significant increase. Change in transaminase, serum albumin & INR was significantly different between acute and chronic hepatitis.

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