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RESEARCH ARTICLE

A COMPARATIVE STUDY OF THE PREVALENCE OF AND RISK FACTORS FOR HEPATITIS-B VIRUS (HBV) AND HEPATITIS-C (HCV) INFECTIONS IN PATIENTS OF CHRONIC RENAL FAILURE UNDERGONING RENAL REPLACEMENT THERAPY- A PROSPECTO-RETROSPECTIVE THERAPY

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ABSTRACT

Context: Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are important causative agents of liver dysfunction in patients with chronic renal failure on renal replacement therapy and that leads to the one of the important causes of morbidity and mortality in this group of patients. **Aims**: To determine the prevalence, risk factors and outcome of HBV and HCV infection among patients with chronic renal failure undergoing renal replacement therapy at the renal unit of Christian Medical College and Hospital, Ludhiana. **Setting and design:** Hospital based Prospecto-retrospective study. **Materials & Methods**: The patients were selected from the Nephrology and Gastroenterology unit Christian Medical College & Hospital, Ludhiana. A total of 449 patients were selected out of which 27 patients were positive for HBs Ag and 18 for anti-HCV making it a total of 43 positive cases and 456 negative cases. 2 patients had co-infection with both HBV and HCV. **Results:** Of the total 449 patients selected only 43 patients was infected with HBV (6.45%,PD, 5.41% HD , and 12.1% RT)and HCV(4.83% PD,3.61 HD and 6.1% RT). The prevalence of HBV and HCV among the patients who had undergone peritoneal dialysis was slightly higher than the figures for patients who had undergone hemodialysis. A good correlation was observed between prevalence of HBV and HCV infection with all 3 variables namely – number of blood transfusions, duration of dialysis and number of dialysis. Overall only around 7% of the patients could clear off the infection. Prevalence of HBV and HCV infection correlated with duration of dialysis, number of dialysis and number of blood transfusions. A significant percentage of patients died of causes other than liver disease. A higher percentage of renal transplant recipients developed cirrhosis compared to patients on hemodialysis. **Conclusion**: A good correlation was observed between prevalence of HBV and HCV infection with all 3 variables namely – number of blood transfusions, duration of dialysis and number of dialysis. Overall only around 7% of the patients could clear off the infection. Prevalence of HBV and HCV infection correlated with duration of dialysis, number of dialysis and number of blood transfusions. A significant percentage of patients died of causes other than liver disease. A higher percentage of renal transplant recipients developed cirrhosis compared to patients on hemodialysis. Outcome of infection in subgroup with peritoneal dialysis was better than that of hemodialysis patients.

INTRODUCTION

One of the important causes of morbidity and mortality in patients with chronic renal failure on renal replacement therapy (dialysis and renal transplantation) is liver dysfunction. Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) are important causative agents of liver dysfunction in these patients (Pereira *et al*, 1997).The prevalence of these viruses amongst the dialysis population varies widely. In India, the prevalence of HBV in the dialysis population is reported to be between 3.4 – 42% and that of HCV between 12.1 – 45.2% (Gupta *et al*, 1996 and Arankalle, 1998). The prevalence of these viruses in the dialysis population is higher than their prevalence in the general population (Jha *et al*, 2000).

Important modes of transmission for these viruses in these patients include horizontal transmission from contaminated machines or disposable objects in the dialysis unit and transfusion of contaminated blood products (Jha *et al*, 2000). In case of HBV, correlation was found between the number of units of blood transfused and the duration of hemodialysis. Hence it was recommended that dialysis machines for HBs Ag positive patients should be segregated from those used for HBs Ag negative patients in addition to following universal precautions and standard infection control measures (Martin *et al*, 1995). Vaccination of HBs Ag negative patients has been recommended and found to be responsible for a significant reduction in the risk of acquiring HBV infection in the developed countries. Patients of chronic renal failure on

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hemodialysis who acquire HBV infection have a high probability of developing chronic hepatitis B as compared to normal immune-competent persons. This is partly due to depressed cell mediated immunity in these patients (Martin *et al*, 1995). Chronic hepatitis B in turn can progress to cirrhosis and hepatocellular carcinoma.

Similarly direct association has been reported between the prevalence of anti HCV Ab and the number of blood transfusions amongst these patients. Duration of hemodialysis is another risk factor for HCV infection in these patients (Roth, 1995). Mode of therapy is another independent risk factor for HCV infection. Patients on hemodialysis have been found to have a higher prevalence than those on CAPD. This appears to be related to a lower requirement for blood transfusion in these patients, absence of a blood access site and domiciliary location of this therapy (Pereira *et al*, 1997).HCV infection, as in immune-competent persons, in patients of chronic renal failure on hemodialysis is characterized by a high rate of chronicity.

However unlike the former, the latter have a higher probability of having chronic viremia without associated biochemical evidence of hepatic dysfunction. Moreover, in these patients, clinical and biochemical features cannot predict severity of histological liver injury and liver biopsy is the most accurate method for that (Martin *et al*, 1995).In case of anti HCV Ab positive patients however, the outcome of infection after renal transplantation is similar to those who are anti HCV Ab negative in the first decade after transplantation (Goffin *et al*, 1995). The present study has been carried out to determine the prevalence of HBV and HCV infection among patients with chronic renal failure undergoing renal replacement therapy at the renal unit of Christian Medical College and Hospital, Ludhiana. It has also been attempted to study the risk factors for HBV and HCV infection in these patients and the outcome of infection, wherever possible.

Modes of Transmission of HBV

Man is the only known natural reservoir for HBV. Hepatitis B Virus Surface Antigen (HBs Ag) has been detected in various body fluids (urine, bile, sweat, semen, tears, vaginal secretions, breast milk, synovial fluid and cerebrospinal fluid) in addition to blood. In developed countries, where there is a relatively low prevalence of HBV, majority of the infections take place in adolescence and adulthood (Chawla, 1996 and Shankar *et al*, 1998).Probability of acquiring infection of proportional to the number of units transfused but administration of blood derivatives and plasma fractions like clotting factor concentrates, cryoprecipitate and fibrinogen can lead to transmission of the virus. (Shankar *et al*, 1998 and Chawla, 1996).

Prevalence of HBV in General Population

It has been estimated that the prevalence rate of HBV (detected by the presence of HBs Ag in the serum using a third generation ELISA) in India is 3-5% (Shankar *et al*, 1998). This is believed to be on an average 4.7% (Thyagarajan *et al*, 1996). India falls in an intermediate zone of HBV prevalence (Guptan *et al*, 1996).

Prevalence of HBV in Dialysis Patients

Across the world, prevalence of HBV infection among patients on hemodialysis varies widely, being as low as < 5% in the USA and as high as 30-40% in the lesser developed countries including India (Sharma *et al*, 1999). Fraser *et al* (1987) reported an incidence and prevalence of HBV infection in a hemodialysis unit in Israel as 25% and 41% respectively. In India, the prevalence of HBV among hemodialysis patients ranges between 3.4-45% (Guptan *et al*, 1996 and Jha *et al*, 2000). A study from Madras found a 7.8% prevalence rate of HBs Ag among patiens who underwent dialysis and/or renal transplantation – 104 out of the 1339 patients testing positive for HBs Ag (Bhaskaran *et al*, 1992).

Modes of Transmission of HCV

Though transfusion of blood and blood products is the most important route for HCV transmission, other parentral and non-paentral routes have been identified. In almost two thirds of cases, transmission of HCV occurs via the parentral route and this route has been most thoroughly studied (Esteban, 1998).Prevalence of HCV is higher in high risk groups like thalassemia, health care workers, i/v drug abusers, and patients on chronic renal failure especially those on maintenance hemodialysis (Esteban, 1998).

Nosocomial transmission is likely to become an important mode of transmission in hospitalized patients is the coming years when there is likely to be a further reduction in the incidence of transmission through blood and blood products. Patient to patient transmission has already been documented especially in cases where there is no history of transfusion or other obvious modes of transmission (Esteban, 1998 and Bruguera *et al*, 2000).

Prevalence of HCV in General Population

In case of HCV, the prevalence worldwide is believed to be 0.04-26% (Esteban, 1998). There is a marked geographical variation in the prevalence rates of HCV infection. The prevalence is the least in developed countries like the USA (1.8%) and European countries (2-3% in Spain, 1.5% in France). The total number of individuals worldwide who are infected with HCV is estimated to be between 150-170 million. The seroprevalence of HCV in India has been estimated to be 1.85% (Panda *et al*, 1998).

Prevalence of HCV in Dialysis Patients

In case of HCV**,** the worldwide prevalence among dialysis patients is believed to be in the range of < 1% to as high as 76% depending upon the region and method used for detection. Now third generation ELISA testing is available, not much comparative data is available. Studies in North America between 1989 and 1993 using first generation ELISA estimated

the prevalence of HCV between 8.36%. Zeldis *et al* (1990) from California, USA found 16 out of the 102 patients studied (15.7%) to be serologically positive for HCV. The CDC in USA carried out a multi-centric prospective study of 499 patients on maintenance hemodialysis and detected an anti HCV Ab positivity rate of 10% (Nie *et al*, 1993).

Aims Of The Study

To study the prevalence of infection with HBV and HCV in patients with chronic renal failure undergoing dialysis and/or renal transplantation, the risk factors for infection with HBV and HCV and to look for the outcome of infection with HBV and HCV.

MATERIALS AND METHODS

This study was a combined retrospective and prospective study where the total study period was 4 years out of which there were 3 years of retrospective and 1 year of prospective study. A total of 499 patients with chronic renal failure who underwent dialysis and/or renal transplantation at the Department of Nephrology and Gastroenterology, Christian Medical College and Hospital, Ludhiana between 1st September 2009 and 31st August 2013. The patients who came between 1st September 2009 and 31st August 2013 comprised the retrospective group and those between 1st September 2013 and 31st August 2014 comprised the prospective group.

For the patients in the retrospective group, the hospital records were studied and data collected including a history and physical examination (general physical and systemic). Renal function tests and liver function tests and serological tests for HBV and HCV were performed in all patients. Wherever possible, the patients were followed up for a period of 6 months and biochemical and serological tests repeated whenever required. Other relevant data was also collected as in the case of retrospective group. Qualitative third generation enzyme linked immunosorbent assay (ELISA) kits (ORTHO) were used to detect the presence of Hepatitis B surface antigen (HBs Ag) and anti HCV antibody (anti HCV Ab) in the sera obtained from these patients. In case of the latter the ELISA kit detected the presence of antibodies to 3 recombinant antigens c22-3, c200 and NS5 of the viral genome of HCV. Prevalence of infection (HBV and/or HCV) was defined as the total number of infected cases (old as well as new) during the study period per 100 patients with chronic renal failure on renal replacement therapy (dialysis and/or transplantation).Analysis was done to check for correlation of prevalence of infection versus each of the three observed variables – number of blood transfusions, duration of dialysis and number of dialysis.

Outcome of Infection: Outcome of infection was assessed as follows:

1. Spontaneous resolution – patients who were infected with HBV and/or HCV (HBs Ag and/or anti HCV Ab positive) initially but became negative later
2. Chronic HBV infection – patients with HBV infection (HBs Ag positive) who continued to be HBs Ag positive after 6 months and they were further divided into 2 groups:
   - Those with no evidence of liver disease [no clinical features of liver disease and normal values of AST / ALT (<40 IU/L)]
   - Those with evidence of liver disease [clinical/histological features of liver disease and/or elevated AST/ALT (>40 IU/L)].
3. Chronic HCV infection – patients with HCV infection (anti HCV Ab positive) who continued to be anti HCV Ab positive after 6 months. And they were further divided into 2 groups:
   - Those with normal ALT (< 40 IU/L)
   - Those with elevated ALT (> 40 IU/L)
4. Cirrhosis – patients with HBV and/or HCV infection who developed clinical/ biochemical/ sonographic/ histological features of cirrhosis.
5. Hepatocellulr carcinoma – Patients with HBV and/or HCV infection who developed clinical/biochemical/ sonographic/ histological features of HCC.
6. Death – This was classified as death due to liver failure and that due to other causes (for example renal failure).
7. Inconclusive – Patients with HBV and/or HCV infection in whom the data was insufficient for assessing the outcome of infection.

Data analysis

The data collected was analyzed using student t-test to look for any statistical difference in the observed values of biochemical tests as well as other data regarding blood transfusions and number and duration of dialysis. A probability value < 0.005 was considered statistically significant. Spearman's rank order correlation co-efficient was used to check for any correlation between observed variables and outcome of infection.

Observations and Results

We carried out a combined retrospective and prospective study on all patients with chronic renal failure/end stage renal disease coming to our hospital for dialysis and/or renal transplantation. The total number of patients in the study was 499.

Out of these 27 patients were positive for HBs Ag and 18 for anti HCV Ab making it a total of 43 positive cases and 456 negative cases. 2 patients had co-infection with both HBV and HCV.

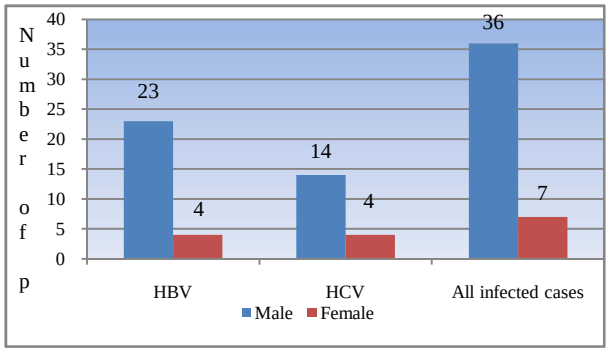
Sex Distribution

Sex distribution among patients in the positive and negative groups was as follows:

1. HBV infected patients – 23 males and 4 females.
2. HCV infected patients – 14 males and 4 females
3. All (HBV/HCV) infected patients – 36 males and 7 females.
4. Negative patients – 308 males and 148 females.

Age Distribution

The age distribution was analyzed in the positive and negative groups:



Graph 1 Sex Distribution of HBV/HCV Infected Cases

The mean age of HBV infected patients was 48.74 years with a range of 14 to 75 years. The mean age of HCV infected patients was 54.06 years with a range of 27 to 66 years. The mean age of all infected (HBV/HCV) patients was 50.28 years with a range of 14 to 75 years. The mean age of negative patients was 51.24 years with a range of 7 to 88 years. A student t-test was applied to check for significant difference in the mean age of patients in patient groups –HBV infected and uninfected, HCV infected and uninfected, infected and uninfected. The p value for these 3 analyses was 0.419, 0.444 and 0.697 respectively. Hence there was no significant difference in the age of patients in positive and negative groups.

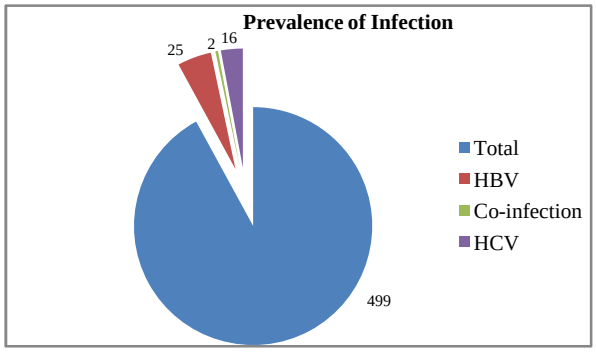
Prevalence of Infection

Hemodialysis

The prevalence of the various subgroups was as follows:

1. Patients with HBV infection (27/499) – 5.41%
2. Patients with HCV infection (18/499) – 3.61%
3. Combined prevalence of HBV & HCV (43/499) – 8.62%
4. Negative cases (456/499) – 91.38%

All patients who underwent peritoneal dialysis or renal transplantation had undergone hemodialysis at some point of time.



Graph 3 Prevalence of HBV/HCV in Transplant Recipients

Peritoneal Dialysis

The number of patients who underwent peritoneal dialysis was 62 (12.42%). Out of these, 4 patients were infected with HBV and 3 with HCV. 1 patient had co-infection with HBV and HCV. The prevalence of the various subgroups in the patients with peritoneal groups was:

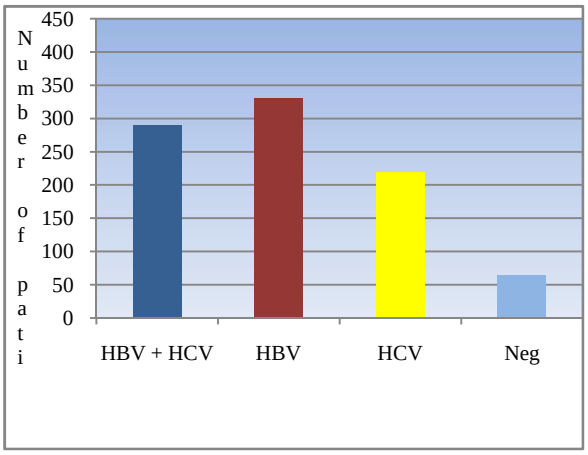
1. Patients with HBV infection (4/62) – 6.45%
2. Patients with HCV infection (3/62) –4.83%
3. Combined prevalence of HBV and HCV (6/62) – 9.68%
4. Negative cases (56/62) – 90.32%

Data collected for these patients in the form of duration of dialysis, number of blood transfusions received and number of times dialysis done as well as values of liver enzymes was statistically analyzed.

Duration of Dialysis

The data analyzed with respect to the duration of dialysis for each of the various subgroups was:

1. The mean duration of dialysis in HBV infected patients was 329.74 days with a range of 1 to 1595 days.
2. The mean duration of dialysis in HCV infected patients was 218.17 days with a range of 3 to 744 days.
3. The mean duration of dialysis in infected (HBV/HCV) patients was 289.02 days with a range of 1 to 1595 days.
4. The mean duration of dialysis in uninfected patients was 64.83 days with a range of 1 to 1500 days.



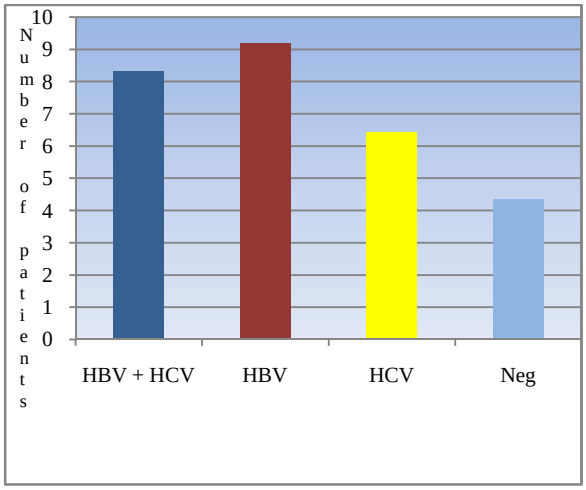
Category Graph 4 Duration of Dialysis

A student t-test was applied to find out the level of significance, if any, between the mean duration among patient groups –HBV infected and uninfected, HCV infected and uninfected and infected and uninfected.

A statistically significant difference was found in each of the three analyses done mentioned above with the p value being < 0.001 for each of them. Hence the patients infected with HBV and/or HCV had been on dialysis for a longer time as compared to negative patients.

Number of Blood Transfusions: The data analyzed with respect to the number of blood transfusions received by patients in each of the various subgroups was:

1. The mean number of blood transfusions received by HBV infected patients was 9.19 with a range of 0 to 45.
2. The mean number of blood transfusions received by HCV infected patients was 6.44 with a range of 0 to 17.
3. The mean number of blood transfusions received by all infected (HBV/HCV) patients was 8.30 with a range of 0 to 45.
4. The mean number of blood transfusions received by negative patients was 4.36 with a range of 0 to 46.



Category Graph 5 Number of Blood Transfusions

A student t-test was applied to check for significant difference in the mean number of blood transfusions between patient groups –HBV infected and uninfected, HCV infected and uninfected and infected and uninfected

A statistically significant difference was found between groups: HBV infected and uninfected and infected and uninfected. The p value was < 0.001 for the above two groups. Thus, HBV infected patients and infected patients (HBV/HCV) had received more number of blood transfusions as compared to negative patients.

However, no statistical difference was found between groups 2 & 4. The p value was 0.150 (> 0.05). Hence there was no significant difference in the number of transfusions received by HCV infected patients and negative patients.

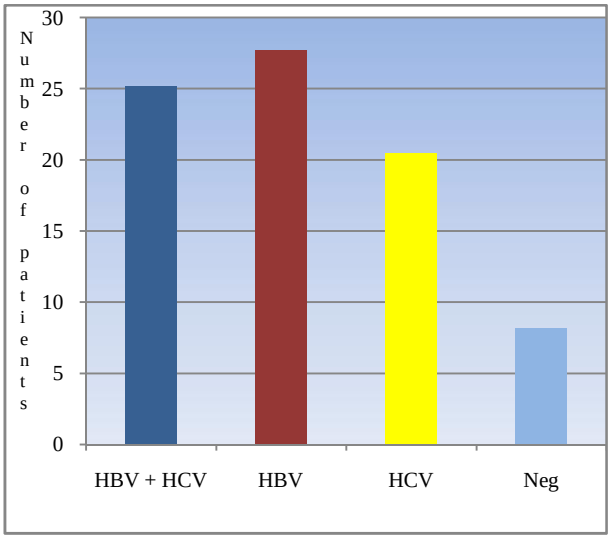
Number of Dialysis

The data analyzed with respect to the number of dialysis of each of the various subgroups was:

1. The mean number of dialysis in HBV infected patients was 27.74 with a range of 1 to 154.
2. The mean number of dialysis in HCV infected patients was 20.44 with a range of 3 to 91.
3. The mean number of dialysis in all infected (HBV/HCV) patients was 25.14 with a range of 1 to 154.
4. The mean number of dialysis in negative patients was 8.14 with a range of 1 to 87.

A student t-test was applied to check for significant difference in the mean number of dialysis done for patients in patient groups – HBV infected and uninfected, HCV infected and uninfected and infected and uninfected.

A statistically significant difference was found in each of the three analyses done mentioned above with the p value being < 0.001 for each of them. Hence the patients infected with HBV and/or HCV had got more number of dialysis as compared to negative patients.



Category Graph 6 Number of Dialysis

Liver Enzymes

The patients in the positive and negative groups were analyzed with respect to the observed values of the 4 liver enzymes namely – AST, ALT, ALP & GGT.

AST

The following are the observed values:

1. The mean value of AST in HBV infected patients was 84.40 IU/L with a range of 9 to 338 IU/L.
2. The mean value of AST in HCV infected patients was 64.96 IU/L with a range of 14 to 106.5 IU/L.
3. The mean value of AST in all infected (HBV/HCV) patients was 68.18 IU/L with a range of 9 to 338 IU/L.
4. The mean value of AST in negative patients was 57.89 IU/L with a range of 2 to 2415 IU/L.

A student t-test was applied to check for significant difference in the mean value of AST in patients groups – HBV infected and uninfected, HCV infected and uninfected and infected and uninfected.

The p value for the 3 analyses were 0.455, 0.875 and 0.714 respectively. All the values were thus more than 0.05 and hence not statistically significant. Therefore, there was no significant difference in the AST values in positive and negative patients.

ALT

The following are the observed values

1. The mean value of ALT in HBV infected patients was 88.08 IU/L with a range of 6 to 448 IU/L.
2. The mean value of ALT in HCV infected patients was 56.51 IU/L with a range of 8 to 110 IU/L.
3. The mean value of ALT in all infected (HBV/HCV) patients was 71.41 IU/L with a range of 6 to 448.25 IU/L.
4. The mean value of ALT in negative patients was 63.37 IU/L with a range of 3 to 3480 IU/L.

A student t-test was applied to check for significant difference in the mean value of ALT in patients groups – HBV infected and uninfected ,HCV infected and uninfected and infected and uninfected. The p value for the 3 analyses were 0.776, 0.910 and 0.834 respectively. All the values were thus more than 0.05 and hence not statistically significant. Therefore, there was no significant difference in the ALT values in positive and negative patients.

ALP

The following are the observed values:

1. The mean value of ALP in HBV infected patients was 286.37 IU/L with a range of 100 to 967 IU/L.
2. The mean value of ALP in HCV infected patients was 257.76 IU/L with a range of 87 to 881.5 IU/L.
3. The mean value of ALP in all infected (HBV/HCV) patients was 255.43 IU/L with a range of 87 to 967 IU/L.
4. The mean value of ALP in negative patients was 223.23 IU/L with a range of 8 to 2081 IU/L.

A student t-test was applied to check for significant difference in the mean value of ALP in patients groups HBV infected and uninfected, HCV infected and uninfected and infected and uninfected. The p value for the 3 analyses were 0.357, 0.484 and 0.318 respectively. All the values were thus more than 0.05 and hence not statistically significant. Therefore, there was no significant difference in the ALP values in positive and negative patients.

Table 1 Combined HBV/HCV Data Analysis

S.No	Parameters	HBs Ag pos/ anti HCV Ab pos patients	HBs Ag pos/ anti HCV Ab neg patients	Probability values
1	No. of patients	43	456	
2	Age (in years ± SEM)	50.28 ± 2.29	51.24 ± 0.72	0.697
3	Male/Female	36/7	308/148	
4	No. of blood transfusions (± SEM)	8.30 ± 1.64	4.36 ± 0.28	< 0.001
5	Duration of dialysis (in days ± SEM)	289.02 ± 58.91	64.83 ± 8.06	< 0.001
6	No. of times dialysis done (± SEM)	24.14 ± 5.10	8.14 ± 0.45	< 0.001
7	Renal Transplantation	12	54	
8	AST (IU/L ± SEM)	68.18 ± 11.52	57.89 ± 8.85	0.714
9	ALT (IU/L ± SEM)	71.41 ± 14.39	63.37 ± 12.09	0.834
10	ALP (IU/L ± SEM)	255.43 ± 27.48	223.23 ± 9.63	0.318
11	GGT (IU/L ± SEM)	103.47 ± 19.89	58.86 ± 4.44	0.002

Table 2 Data Analysis

S.No	Parameters	HBs Ag pos	HBs Ag pos/ anti HCV Ab neg patients	Probability values
1	No. of patients	27	456	
2	Age (in years ± SEM)	48.74 ± 3.39	51.24 ± 0.72	0.419
3	Male/Female	23/4	308/148	
4	No. of blood transfusions (± SEM)	9.19 ± 12.53	4.36 ± 0.28	< 0.001
5	Duration of dialysis (in days ± SEM)	329.74 ± 91.23	64.83 ± 8.06	< 0.001
6	No. of times dialysis done (± SEM)	27.74 ± 7.65	8.14 ± 0.45	< 0.001
7	Renal Transplantation	8	54	
8	AST (IU/L ± SEM)	84.40 ± 17.32	57.89 ± 8.85	0.455
9	ALT (IU/L ± SEM)	88.08 ± 21.88	63.37 ± 12.09	0.776
10	ALP (IU/L ± SEM)	286.37 ± 43.17	223.23 ± 9.63	0.357
11	GGT (IU/L ± SEM)	101.34 ± 17.61	58.86 ± 4.44	0.009

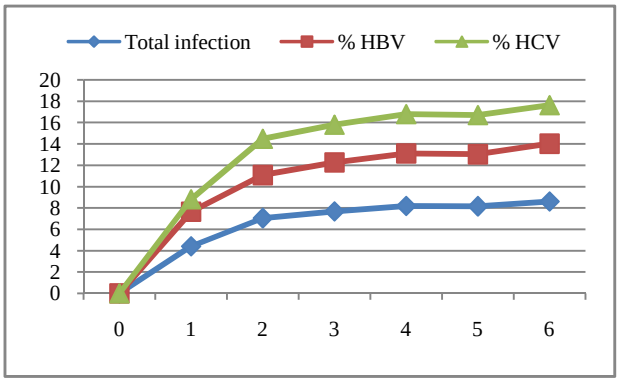
Table 3HCV Data Analysis

S.No	Parameters	Anti HCV Ab pos	HBs Ag pos/ anti HCV Ab neg patients	Probability values
1	No. of patients	18	456	
2	Age (in years ± SEM)	54.06 ± 2.41	51.24 ± 0.72	0.444
3	Male/Female	14/4	308/148	
4	No. of blood transfusions (± SEM)	6.44 ± 1.32	4.36 ± 0.28	0.150
5	Duration of dialysis (in days ± SEM)	218.17 ± 41.28	64.83 ± 8.06	< 0.001
6	No. of times dialysis done (± SEM)	20.44 ± 4.86	8.14 ± 0.45	< 0.001
7	Renal Transplantation	4	54	
8	AST (IU/L ± SEM)	64.96 ± 18.93	57.89 ± 8.85	0.875
9	ALT (IU/L ± SEM)	56.51 ± 15.85	63.37 ± 12.09	0.910
10	ALP (IU/L ± SEM)	257.76 ± 45.81	223.23 ± 9.63	0.484
11	GGT (IU/L ± SEM)	128.57 ± 42.43	58.86 ± 4.44	0.004

GGT

The following are the observed values

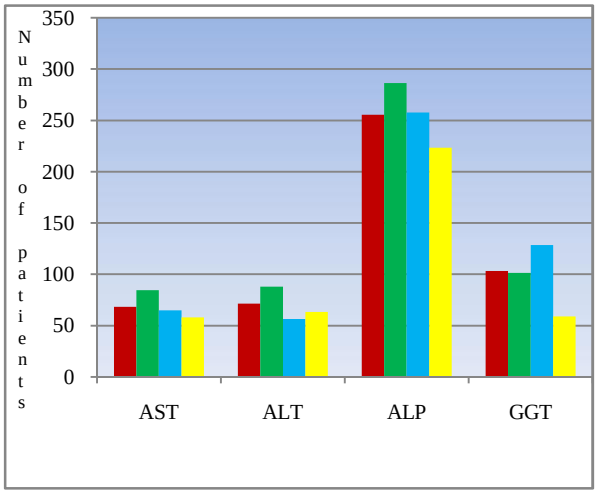
1. The mean value of GGT in HBV infected patients was 101.34 IU/L with a range of 20 to 328.5 IU/L.
2. The mean value of GGT in HCV infected patients was 128.57 IU/L with a range of 15 to 762 IU/L.
3. The mean value of GGT in all infected (HBV/HCV) patients was 103.47 IU/L with a range of 15 to 762 IU/L.
4. The mean value of GGT in negative patients was 58.86 IU/L with a range of 5 to 706 IU/L.



No. of Transfusions	Total cases	Total infected cases	HBV cases	HCV cases	%Total Infected Cases	% HBV cases	% HCV cases
0	0	0	0	0	0	0	0
10	310	31	20	13	10	6.451613	4.193548
20	352	40	24	18	11.36364	6.818182	5.113636
30	363	41	25	18	11.29477	6.887052	4.958678
40	370	43	27	18	11.62162	7.297297	4.864865
Correlation between no. of blood transfusions and infection					0.851573	0.970578	0.591222

A student t-test was applied to check for significant difference in the mean value of GGT in patients groups – HBV infected and uninfected, HCV infected and uninfected and infected and uninfected.

The p value for the 3 analyses were 0.009, 0.004 and 0.002 respectively. All the values were thus less than 0.05 and hence statistically significant. Therefore, positive patients (HBV and/or HCV infected) had higher values of GGT in comparison to negative (non-infected) patients.



Biochemical Values Graph 7 Liver Enzymes

Higher mean values of AST and ALT were observed in HBV infected patients in comparison to HCV infected patients. The analysis was done after excluding the data from the 2 patients who had coinfection with HBV and HCV. The observed difference in the mean values between the two groups was however not statistically significant. As mentioned earlier, there was no significant difference in the mean values of AST and ALT among positive (HBV and/or HCV) and negative patient groups.

Correlation of Parameters with Prevalence of Infection

Data obtained from HBV and HCV infected patients was analyzed to look for any correlation between: Duration of dialysis and Prevalence of infection, number of blood transfusions and Prevalence of infection and number of dialysis and Prevalence of infection

This was done using Pearson's correlation coefficient.

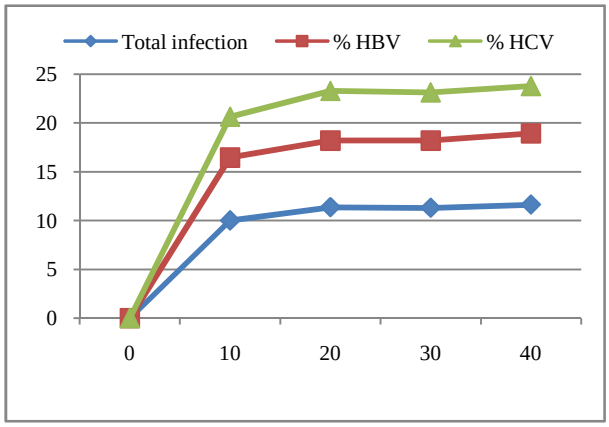
A good correlation was seen between infection and the above three variables. The values of correlation coefficient were as follows:

- Duration of dialysis and combined prevalence of infection (HBV/HCV) – 0.865
- Duration of dialysis and prevalence of HBV infection – 0.955

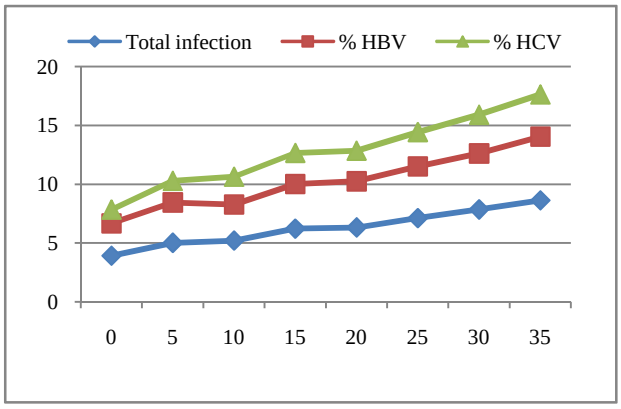
Table 4 Prevalence of Infection and Duration of Dialysis

No.of 6 months of Dialysis	Total Cases	Total Infected Cases	HBV cases	HCV cases	% Total Infection	% HBV cases	% HCV cases	% HBV/ infected cases	% HCV/ Infected cases
0	0	0	0	0	0	0	0	0	0
1	431	19	14	5	4.408353	3.24826	1.160093	73.68421	26.31579
2	469	33	19	16	7.036247	4.051173	3.411514	57.57576	48.48485
3	481	37	22	17	7.692308	4.573805	3.534304	59.45946	45.94595
4	488	40	24	18	8.196721	4.918033	3.688525	60	45
5	491	40	24	18	8.14664	4.887984	3.665988	60	45
6	499	43	27	18	8.617234	5.410822	3.607214	62.7907	41.86047
Correlation between duration of dialysis and infection					0.864721	0.954789	0.707584		

- Duration of dialysis and prevalence of HCV infection – 0.708
- Number of blood transfusions and combined prevalence of infection (HBV/HCV) – 0.852.
- Number of blood transfusions and prevalence of HBV infection – 0.971.
- Number of blood transfusions and prevalence of HCV infection – 0.591.
- Number of dialysis and combined prevalence of infection (HBV/HCV) – 0.991.
- Number of dialysis and prevalence of HBV infection – 0.967.
- Number of dialysis and prevalence of HCV infection – 0.970.



No. of Dialysis	Total Cases	Total Infected Cases	HBV cases	HCV cases	% Total Infection	% HBV cases	% HCV cases	% HBV/ infected cases	% HCV/ Infected cases
0	0	0	0	0	0	0	0	0	0
5	255	10	7	3	3.921569	2.745098	1.176471	70	30
10	379	19	13	7	5.013193	3.430079	1.846966	68.42105	36.84211
15	423	22	13	10	5.200946	3.073286	2.364066	59.09091	45.45455
20	450	28	17	12	6.222222	3.777778	2.666667	60.71429	42.85714
25	459	29	18	12	6.318083	3.921569	2.614379	62.06897	41.37931
30	478	34	21	14	7.112971	4.393305	2.92887	61.76471	41.17647
35	484	38	23	16	7.85124	4.752066	3.305785	60.52632	42.10526
40	499	43	27	18	8.617234	5.410822	3.607214	62.7907	41.86047
Correlation between number of dialysis and infection					0.990839	0.966867	0.969601		



Outcome of Infection in Hemodialysis Patients

Combined HBV/HCV Infected Patients

In all the outcome of the 43 infected patients put together was as follows:

Table 7 Outcome in HBV/HCV infected Dialysis Patients

S.No	Outcome in HBV/HCV infected Dialysis Patients	Number	Percentage
1	Spontaneous Resolution	3	6.98
2	Chronic HBV/HCV infection	19	44.19
3	Cirrhosis	3	6.98
4	Hepatocellular carcinoma	0	0
5	Death due to liver failure	2	4.65
6	Death due to other causes	8	18.60
7	Inconclusive	8	18.60
	Total	43	100

3Patients had spontaneous resolution.19 patients developed chronic HBV/HCV infection.3 patients developed cirrhosis. No patient developed HCC. 2 patients died of liver failure. 8 patients died of other causes. In 8 patients the outcome was inconclusive.

HBV infected Patients

For the 27 HBV infected patients, the outcome was as follows: 2 Patients had spontaneous resolution.7 patients developed chronic HBV infection without liver disease.4 patients developed chronic HBV infection with liver disease.3 Patients developed cirrhosis. No patient developed HCC.1 patient died of liver failure.6 patients died of other causes. In 4 patients the outcome was inconclusive. Two patients underwent liver biopsy – one had histological features of chronic hepatitis and the other of cirrhosis. 5 patients were positive for Hepatitis B e Antigen (HBe Ag) out of which 3 had chronic HBV infection without liver disease, 1 had chronic HBV infection with liver disease (chronic hepatitis on liver histology as well as elevated AST/ALT) and 1 had cirrhosis.

Table 8 Outcome in HBV infected Dialysis Patients

S.No	Outcome in HBV infected Dialysis Patients	Number	Percentage
1	Spontaneous Resolution	2	7.41
2	Chronic HBV infection without liver disease	7	25.93
3	Chronic HBV infection with liver disease	4	14.81
4	Cirrhosis	3	11.11
5	Hepatocellular carcinoma	0	0
6	Death due to liver failure	1	3.70
7	Death due to other causes	6	22.22
8	Inconclusive	4	14.81
	Total	27	100

HCV Infected Patients

For the 18 HCV infected patients, the outcome was as follows:

- 1 patient had spontaneous resolution of infection

- 7 patients developed chronic HCV infection with normal ALT values.
- patients developed chronic HCV infection with elevated ALT values
- No patient developed cirrhosis
- No patient developed HCC.
- 1 patient died of liver failure
- 2 patients died of other causes
- In 4 patients the outcome was inconclusive.

Table 9 Outcome in HCV Infected Dialysis Patients

S.No	Outcome in HCV infected Dialysis Patients	Number	Percentage
1	Spontaneous Resolution	1	5.56
2	Chronic HCV infection with normal ALT	7	38.89
3	Chronic HCV infection with elevated ALT	3	16.67
4	Cirrhosis	0	0
5	Hepatocellular carcinoma	0	0
6	Death due to liver failure	1	5.56
7	Death due to other causes	2	11.11
8	Inconclusive	4	22.22
	Total	27	100

One patient who had chronic HCV infection with elevated ALT values died of liver failure. Liver biopsy was done in one patient (vide supra), which showed histological features of chronic hepatitis.

Outcome of Infection in Patients with Renal Transplant

Combined HBV/HCV Infected patients

In all the outcome of the 12 infected patients put together was as follows:

- patients had spontaneous resolution of infection.
- patients developed chronic HBV/HCV infection.
- 2 patients developed cirrhosis
- No patient died of liver failure or due to other causes.

HBV infected Patients

For the 8 HBV infected patients, the outcome was a follows:

- 2 patients had spontaneous resolution
- patients developed chronic HBV infection without liver disease
- No patient developed chronic HBV infection with liver disease.
- 2 patients developed cirrhosis.
- No patient died of liver failure or due to other causes.

HCV infected Patients

For the 4 HCV infected patients, the outcome was as follows

- 1 patient had spontaneous resolution of infection
- 1 patient developed chronic HCV infection with normal ALT.
- No patient developed chronic HCV infection with elevated ALT.
- No patient developed cirrhosis
- No patient died of liver failure or due to other causes.
- In 2 patients the outcome was inconclusive.

Outcome of Infection in Peritoneal Dialysis Patients

Combined HBV/HCV Infected In all the outcome of the 6 infected patients but together was as follows:

- 2 patients had spontaneous resolution of infection.
- 2 patients developed chronic HBV / HCV infection.
- No patient developed cirrhosis.
- No patient died of liver failure
- 2 patients died of other causes

HBV Infected Patients

For the 4 HBV infected patients, the outcome was as follows:

- 2 patients had spontaneous resolution.
- No patient developed chronic HBV infection without liver disease.
- 1 patient developed chronic HBV infection with liver disease.
- No patient developed cirrhosis.
- No patient died of liver failure.
- 1 patient died of other causes.

HCV infected Patients.

For the 3 HCV infected patients, the outcome was as follows:

- No patient had spontaneous resolution of infection
- 1 patient developed chronic HCV infection with normal ALT.
- 1 patient developed chronic HCV infection with elevated ALT.
- No patient developed cirrhosis
- No patient died of liver failure
- 1 patient died of other causes.

Table 10 Outcome in infected patients (Combined).

S.No.	Outcome in infected patients (Combined)	Number with RT	% in RT	Number with PD	% in PD
1	Spontaneous Resolution	3	25	2	33.33
2	Chronic HBV/HCV infection	5	41.67	2	33,33
3	Cirrhosis	2	16.67	0	0
4	Hepatocellular carcinoma	0	0	0	0
5	Death due to liver failure	0	0	0	0
6	Death due to other causes	0	0	2	33.33
7	Inconclusive	2	16.67	0	0
	Total	12	100	6	100

Table 11 Outcome in HBV infected patients

S.No.	Outcome in infected patients (Combined)	Number with RT	% in RT	Number with PD	% in PD
1	Spontaneous Resolution	2	25.0	2	50.0
2	Chronic HBV infection without liver disease	4	50.0	0	0
3	Chronic HBV infection with liver disease	0	0	1	25.0
4	Cirrhosis	2	25.0	0	0
5	Hepatocellular carcinoma	0	0	0	0
6	Death due to liver failure	0	0	0	0
7	Death due to other causes	0	0	1	25.0
8	Inconclusive	0	0	0	0
	Total	8	100	4	100

Table 12 Outcome in HCV infected patients

S.No.	Outcome in HCV Infected patients	Number with RT	% in RT	Number with PD	% in PD
1	Spontaneous Resolution	1	25.0	0	0
2	Chronic HCV infection with normal ALT	1	25.0	1	33.33
3	Chronic HCV infection with elevated ALT	0	0	1	33.3
4	Cirrhosis	0	0	0	0
5	Hepatocellular carcinoma	0	0	0	0
6	Death due to liver failure	0	0	0	0
7	Death due to other causes	0	0	1	33.3
8	Inconclusive	2	50.0	0	0
	Total	4	100	3	100

Correlation of Parameters and Outcome of Infection

Data was analyzed to look for any correlation between duration of dialysis and outcome of infection using Spearman's rank order correlation coefficient. The following observations were made:

- There was some correlation between duration of dialysis and outcome of infection in HBV infected patients. The correlation co-efficient was 0.417 with a probability value of 0.03.
- No correlation was found between duration of dialysis and outcome of infection in HCV infected patients.
- No correlation was found between duration of dialysis and outcome of infection in HBV/HCV infected patients when analyzed together.

Similarly data was analyzed to look for correlation between number of dialysis and outcome of infection. Again a similar degree of correlation was found between this parameter and outcome of infection in HBV infected patients (Correlation coefficient value of 0.404 with a probability value of 0.04).

No correlation was found between number of dialysis and outcome of infection in HCV infected patients and all infected patients as a whole.

The same statistical method was used to look for any correlation between:

- ALT value and outcome of infection
- GGT value and outcome of infection.

No correlation was found between value of ALT at time of initiation of renal replacement therapy with outcome of infection in HBV infected patients, HCV infected patients and all infected patients as a whole.

A certain degree of correlation was found between GGT value at time of initiation of renal replacement therapy with outcome of infection in HCV infected patients (Correlation coefficient value of 0.630 at a probability value of 0.005). This indicated that patients with high initial GGT values had a worse prognosis in comparison to those who had lower values.

However, a similar correlation could not be observed between GGT value and outcome of infection in either HBV infected patients or all infected patients as a whole.

DISCUSSION

Males outnumbered the females – ratio being slightly more than 2 : 1 for uninfected cases and slightly more than 5 : 1 for infected cases (slightly less than 6 : 1 for HBV infected cases and 3.5 : 1 for HCV infected cases. No statistical difference was found in the mean age of infected patients (HBV infected alone/HCV infected alone/combined infected cases) compared

Table 12 Comparison of studies on HBV prevalence

S. No	Study	Year	Total patients on HD	HBs Ag pos patients	% with HBV infection	Patients with RT	HBs Ag pos RT patients	RT patients with HBV (%)
1	Thomas *et al*	1986	283	119	42	NS	NS	NS
2	Bhaskaran *et al*	1992	1339	104	7.8	455	65	14.29
3	Roy *et al*	1994	NS	NS	NS	383	135	34.4
4	Radhakrishnan *et al*	2000	NS	NS	NS	68	12	17.6
5	Present study	2009	499	27	5.41	66	8	12.1

NS = not studied, RT-Renal transplant.

Table 13 Comparison of studies on HCV prevalence

S. No	Study	Year	Total patients on HD	Anti HCV pos patients	% with HCV infection	Patients with RT	Anti HCV pos RT patients	RT patients with HCV (%)
1	Salunkhe *et al*	1992	31	14	45.2	NS	NS	NS
2	Chadha *et al*	1993	33	4	12.1	NS	NS	NS
3	Sumathy *et al*	1993	8	3	37.5	37	12	32.4
4	Arankalle *et al*	1995	57	14	24.5	NS	NS	NS
5	Jaiswal *et al*	1996	105	44	41.9	NS	NS	NS
6	Agarwal *et al*	2000	NS	NS	NS	128	37	28.9
7	Present study	2009	499	18	3.61	66	4	6.1

NS = not studied

Table 14 Comparison of prevalence in hemodialysis and peritoneal dialysis

Mode of dialysis	Total patients	HBs Ag pos patients	% with HBV infection	Anti HCV pos patients	% with HCV infection	HBV/HCV infected patients	%with HBV/HCV infection
Hemodialysis	499	27	5.41	18	3.61	43	8.62
Peritoneal dialysis	62	4	6.45	3	4.83	6	9.68

to that of uninfected patients. As mentioned in Observations and Results, it was found that 27 patients were infected with HBV (HBs Ag positive) and 18 with HCV (anti HCV Ab positive). 2 patients had coinfection with both HBV and HCV and hence the total number of infected patients was 43. Thus the prevalence of HBV in the study population was 5.41%. This was slightly higher than the prevalence of HBV in the general population of India, which is believed to be 3-5% (Shankar *et al*, 1995), and on an average 4.7% (Thyagarajan *et al*, 1996). The prevalence of HBV among renal transplant recipients in this study was 12.12%, which is similar to the observed prevalence in transplant patients in the country. Bhaskaran *et al* (1992) had reported a 7.8% prevalence of HBV among renal transplant patients in their study. The prevalence of HCV in this study was 3.61%, which is more than the observed prevalence of HCV in the general population of India, believed to be on an average 1.85% (Panda *et al*, 1998).

It is also higher than the observed prevalence in the general population in this part of the country. The prevalence of HCV in this study is less than the observed prevalence of HCV among hemodialysis patients in the country, which is believed to vary from 7-60% (Jha *et al*, 2000).The prevalence of HCV among renal transplant recipients in this study was 6.06%, which is much less than the observed prevalence of the virus in this group of patients across the country. Sumathy *et al* (1993) had found a prevalence of 32.4% among the 37 renal transplant recipients at their center. Agarwal *et al* (2000) had found 28.9% prevalence rate in the transplant population at their center located in a similar part of the country. In fact 8 of the 18 patients (44.4%) who were detected to be anti HCV Ab positive became seropositive after initiation of hemodialysis (Similarly 8 of the 27 HBs Ag positive patients became seropositive after initiation of hemodialysis and totally 19 of the 43 infected patients acquired infection after initiation of hemodialysis).

The prevalence of HBV and HCV among the patients who had undergone peritoneal dialysis was slightly higher than the figures for patients who had undergone hemodialysis. HBV prevalence among those who had received peritoneal dialysis and those on hemodialysis was 6.45% and 5.41% respectively. Similar figures for HCV were 4.83% and 3.61% respectively. Figures for total infected patients were 9.68% and 8.62% respectively. None of the observed differences were statistically significant. Moreover, none of the patients in the peritoneal dialysis group had it as the sole mode of dialysis. All of them had undergone hemodialysis at some point of time. In addition, the number of patients in the peritoneal dialysis group was much smaller than in the group of hemodialysis patients. Therefore the observed higher prevalence figures in the group of patients with peritoneal dialysis do not necessarily contradict the known observations about patients on peritoneal dialysis having lesser prevalence of infection, especially that the HCV, in comparison to those on hemodialysis.

A statistically significant difference was observed in the mean duration of dialysis among infected patients (HBV alond / HCV alone / all infected patients together) in comparison to uninfected patients. This was consistent with the observations made by almost all the authores in different studies worldwide (Niu *et al*, 1993; Cendoroglo Neto *et al*, 1995; Dussol *et al*, 1995; Natov *et al*, 1998).

It was observed that infected patients as a whole had received significantly more number of transfusions in comparison to uninfected patients and so had HBV infected patients (HBs Ag positive) compared to uninfected patients. HCV infected patients (anti HCV Ab positive) patients also had received more transfusions in comparison to uninfected patients but this difference was not found to be statistically significant. Studies by different authors worldwide have shown different observations regarding blood transfusions and HCV infection. Some have shown more number of transfusions in HCV infected patients (Dussol *et al*, 1995 and Natov *et al*, 1998) while others have not made such observations (Niu *et al*, 1993). In the recent study from North India (Agarwal *et al*, 1999), HCV infected patients had received more blood transfusions than other patients. However another study (Salunkhe *et al*, 1992) had not shown any difference in this context.

A good correlation was observed between prevalence of HBV and HCV infection with all 3 variables namely – number of blood transfusions, duration of dialysis and number of dialysis. The correlation was best for HBV with regards to all the three variables – the Pearson's correlation was best for HBV with regards to all the three variables – the Pearson's correlation coefficient being 0.971, 0.955 and 0.967 respectively. There was a very good correlation between HCV infection and number of dialysis (correlation coefficient – 0.970), a good correlation between HCV infection and duration of dialysis (correlation coefficient – 0.708) and some degree of correlation between HCV infection and number of transfusions (correlation coefficient – 0.591).

No statistical difference was found between mean values of AST, ALT and ALT values in infected patients (HBV infected alone/HCV infected alone/combined infected cases) compared to that in uninfected patients. However a difference was found in the mean values of AST and ALT in HBV infected patients in comparison with HCV infected patients. HBV infected patients had higher values but the observed difference was not statistically significant. It was also found that the mean value of GGT was more in infected patients (HBV alone/HCV alone/all infected cases together) compared to that in uninfected patients. Initial value of GGT (value at initiation of renal replacement therapy) correlated with outcome of infection in HCV infected patients but not in HBV infected patients. This observation might be not be insignificant since this enzyme is relatively specific for liver similar to ALT and in contrast to ALP and AST (which can be derived from other organs of the body.

The observation of this study; wherein HBs Ag positive patients alone, anti-HCV patients alone and all infected patients put together had higher mean values of GGT in comparison to patients negative for these serological markers and that initial values of GGT correlated with outcome in HCV infected patients, might require more studies especially on a larger population of infected patients and preferably over a longer period of time to be substantiated and hence put to use in clinical practice.

In terms of outcome of infected patients, it was found that majority of the patients developed chronic infection though a significant percentage (18.6%) died of unrelated causes. Since liver biopsy could be done only in 3 patients and more sensitive molecular techniques (vide supra) could not be done owing to economic constraints, the outcome could not be accurately assessed in some of the patients for which serial biochemical and serological data was not available. Overall only around 7% of the patients could clear off the infection. But the fact that none of the patients developed hepatocellular carcinoma and only around 7% developed cirrhosis, confirms the theory that the time taken for severe liver disease (induced by these viruses) to get manifested is more than the average life expectancy of these patients. Similar observations were made in the groups of HBV infected patients and of HCV infected patients when analyzed separately.

In the subgroup with renal transplant, a higher percentage (25%) had spontaneous resolution of infection which is unusual since such patients would be expected to have a lesser chance of clearing off the infection owing to higher degree of immunosuppression induced by post transplant drug therapy. However the number of patients with transplants was relatively less (12 in number) and hence extrapolation of the same to the general population of renal transplant recipients may not be appropriate. However a greater percentage did develop cirrhosis (around 17%) and the percentage developing chronic infection was similar to the hemodialysis group. Similar results were seen in analysis of the HBV infected group alone. However in case of HCV infected patients, an outcome could not be predicted in half of the patients. This might suggest that the need for a liver biopsy and/or better molecular techniques is more important in HCV infected patients than HBV infected patients than HBV infected patients – thing supported to some extent by the difference (though not statistically significant) in the ean values of AST and ALT in HBV and HCV infected patients (the former having higher values). It is possible that the biochemical values are more useful for HBV and that HCV infected patients because of a difference in the characteristics of liver disease and a possible difference in the immune status induced by the virus are unable to have sustained enzyme elevation.

For the subgroup of patients who underwent peritoneal dialysis, equal number of patients (2 each) had spontaneous resolution, chronic infection and death due to other causes. Half of the HBV infected patients had spontaneous resolution. This might be a reflection of the fact that patients on hemodialysis tend to have a worse prognosis than those on peritoneal dialysis. However in the HCV infected group, none of the patients had spontaneous resolution and majority developed chronic infection – a fact that is consistent with the natural course of HCV infection. These observations of natural course of infection in this group of patients (those with peritoneal dialysis) being similar to that in patients with normal renal functions may suggest that the alteration in immune status induced by end stage renal disease may be less pronounced in patients with peritoneal dialysis in comparison to those on hemodialysis.

SUMMAY AND CONCLUSIONS

HBV and HCV infections are known to occur in patients with end stage renal disease on all forms of renal replacement therapy. This study was conducted on a cohort of 499 patients with chronic renal failure on various forms of renal replacement therapy. The prevalence, risk factors for and outcome of infection with HBV and HCV were studied.

1. Overall 43 patients were detected to be infected with HBV and/or HCV (prevalence of 8.62%). Of these, 27 were infected with HBV (5.41% prevalence) and 18 with HCV (3.61% prevalence). Two patients had co-infection with HBV and HCV.
2. Prevalence of HBV and HCV infection correlated with duration of dialysis, number of dialysis and number of blood transfusions.

- Correlation was best with number of dialysis for both HBV and HCV.
- For HBV, an equally good correlation was observed with duration of dialysis and number of transfusions.
- For HCV, a lesser degree of correlation was observed with duration of dosage and least with number of transfusions.

3. Patients with HBV and/or HCV infection had higher mean values of GGT compared to uninfected patients.
4. Initial values of GGT (values at initiation of renal replacement therapy) correlated with outcome in HCV infected patients. Higher initial values indicated a worse prognosis. Spearman's rank order correlation coefficient was used to check for correlation of GGT with outcome of HCV infection.
5. HBV and HCV infected patients had been on a longer duration of dialysis as well as had undergone more number of dialysis in comparison to uninfected patients. HBV infected patients had received more number of blood transfusions compared to uninfected patients. Therefore, duration of dialysis and number of dialysis were risk factors for HBV/HCV infection. Number of blood transfusions was a risk factor for HBV infectio9n.
6. Majority of infected patients developed chronic HBV/HCV infection.
7. A significant percentage of patients died of causes other than liver disease.
8. A higher percentage of renal transplant recipients developed cirrhosis compared to patients on hemodialysis.
9. Outcome of infection in subgroup with peritoneal dialysis was better than that of hemodialysis patients.

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