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Original Article

Prevalence of occult hepatitis B virus infection in hemodialysis patients in Isfahan, Iran

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Abstract

Background: The absence of a detectable hepatitis B surface antigen (HBsAg) with or without hepatitis B core antibody (anti-HBc) or hepatitis B surface antibody (anti-HBs) in the presence of hepatitis B virus-DNA (HBV-DNA) is defined as occult HBV infection. This study was aimed to evaluate the prevalence of occult HBV infection in patients receiving hemodialysis (HD) in Isfahan, Iran.

Materials and Methods: This cross sectional study was done on 400 patients without acute or chronic HBV infection with end-stage renal disease undergoing regular HD. Blood samples were collected prior to the HD session, and serological markers of viral hepatitis B included HBsAg, anti-HBs and anti-HBc were measured using standard third generation commercially avail-able enzyme immunoassays kit, then samples of positive anti-HBc and negative anti-HBs were tested for HBV DNA using quantitative real-time polymerase chain reaction techniques. Data were analyzed by SPSS using *t*-test and Chi-square test.

Results: The mean age of patients was 51.6 ± 11.2 years. Anti-HBc positive was observed in 32 (8%) of 400 studied patients with negative HBsAg. Of 32 patients with anti-HBc positive, 15 were males and 17 were females with mean age of 49.7 ± 12.6 years. Among 32 patients with anti-HBc positive, 10 patients were negative for anti-HBs. All of 10 patients were negative for HBV DNA. The prevalence of occult HBV infection was 0%.

Conclusions: The prevalence of occult HBV infection in HBsAg negative patients undergoing HD was 0% and look to be among the lowest worldwide. So, occult HBV infection is not a significant health problem in HD patients in this region.

Key Words: Hemodialysis, hepatitis B core antibody, hepatitis B surface antibody, hepatitis B virus DNA, occult hepatitis B

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INTRODUCTION

The risk for infection in chronic hemodialysis (HD) patients because of the process of HD requires vascular access for prolonged periods is high.[1] Surveillance for infections associated with chronic HD has always focused on viral hepatitis. The morbidity and mortality

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of these infections in the dialysis population is difficult to quantify.[2] Hepatitis B virus (HBV) is one of the most well-known and important causes of liver disease in these patients.[3-5] In HD centers, HBV infection rates have significantly reduced after the introduction of HBV vaccine, the isolation strategy for hepatitis B surface antigen (HBsAg) positive patients, the discovery of erythropoietin, and the implementation of infection control measures.[6] Recently, it is reported that the prevalence rates of HBV infection in HD facilities seem to concur more closely with the general population.[7]

Occult HBV infection is defined as the absence of a detectable HBsAg with or without hepatitis B core antibody (anti-HBc) or hepatitis B surface antibody (anti-HBs) in the presence of HBV-DNA.[8] Among HD patients occult HBV infection is also highly prevalent, those undergoing frequent blood transfusions, blood donors, and intravenous drug users.[9-13]

The prevalence of occult HBV infection is related to the overall prevalence of HBV infection in the general population.[14] In published reports in HBsAg negative patients on HD the prevalence of occult HBV infection ranges between 0% and 58%,[4,15-18] whereas in a North American population was reported to be 3.7%,[19] in India, population was reported to be 4.9%,[19] in Italy was reported ranges between 0% and 26.6% in two cohorts,[4,20] and in Turkey prevalence rates of 2.7% and 12.4% have been reported.[21,22] In a study in Iranian HD patients with isolated anti-HBc, the HBV-DNA was detectable in 50% of these patients.[23]

Variations in the prevalence of HBV infection among countries, the size and virological features of the study groups and sensitivity of molecular techniques are among the probable causes of the different frequencies of occult HBV infection in HD patients.[24] Furthermore, the prevalence rate of HBV reported different based on geographic heterogeneity worldwide, and prevalence is especially heterogeneous across Iran. Iran is an area of low endemicity (the carrier rate in low endemicity areas is less than 2% and less than 20% of the population is infected with HBV) and despite the potential clinical importance of occult HBV infection; data about the prevalence of occult HBV infection among Iranian patients undergoing HD is limited. So, the present study was aimed to investigate the prevalence of occult HBV infection in patients receiving HD at a single center in Isfahan, Iran.

MATERIALS AND METHODS

In this cross-sectional study a total of 400 patients with end-stage renal disease undergoing regular HD from nephrology and dialysis units in Kashani, Faiz and Al-Zahra Hospitals in Isfahan, Iran were included between July and January, 2013. This study was investigated and approved by the ethics committee of Isfahan University of Medical Sciences. Patients undergoing HD for at least 6 months in both genders without acute or chronic HBV infection, no history of other liver disease and other risk factors such as human immunodeficiency virus (HIV) were eligible. Furthermore, patients who were being treated with interferon and/or ribavirin and who had family history of HBV infection were not included. After that participating subjects were explained about the purposes of the study written informed consent was obtained.

Collected information were included age, sex, history of previous transfusion, duration of dialysis, tattooing history, history of renal transplantation, history of diabetes mellitus, HBsAg, anti-HBs, and anti-HBc which were evaluated in studied subjects.

Prior to the HD session, blood samples were collected, centrifuged immediately, and the sera were separated, aliquoted, and then stored at −20°C until use. Serological markers of viral hepatitis B (HBsAg, anti-HBs, anti-HBc) were measured using standard third generation commercially avail-able enzyme immunoassays kit (Diapro, Milano, Italy). Also, samples from patient with positive anti-HBc and negative anti-HBs were tested for HBV DNA using quantitative real-time polymerase chain reaction techniques (Diapro, Milano, Italy) with specific prime and probes.

The sample size was calculated with two-sided log-rank test, $\alpha = 0.05$, and 80% power. SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used to managed and analyzed the collected data. Descriptive statistics are reported as mean ± standard deviation, median [interquartile range] or number (percent) as appropriate. Independent sample *t*-test and Chi-square test were used to compare continues and categorical variables, respectively. The significance level was set at less than 0/05.

RESULTS

Characteristics of study population are shown in Table 1. In this study, blood samples were obtained from 400 enrolled HD patients. The mean age of patients studied was 51.6 ± 11.2 years (range: 17–68). Of 400 patients studied, 234 (58.5%) were male and 166 (41.5%) were female. Most of the patients had history of transfusion; nearly 10% of patients reported history of renal transplantation and 33% had diabetes

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mellitus. In all 400 patients studied, anti-HBc positive was observed in 8% of patients (32 of 400) with negative HBsAg. As shown in Table 1 among 32 patients with anti-HBc positive, 15 were males and 17 were females. The mean age was 49.7 ± 12.6 years and the mean dialysis period was 51.3 + 35.6 months. Patients with anti-HBc positive were younger with higher dialysis period than in all patients (51.6 years and 49.1 months). Of anti-HBc positive patients 84% had history of transfusion, 12% had diabetes mellitus and history of renal transplantation was not observed in these patients.

Frequency of various combinations of HBV markers are detailed in Table 2. Among 32 patients with anti-HBc positive, 10 patients were negative for anti-HBs and 22 patients were positive. HBV DNA was assessed in patients with anti-HBs negative and results showed that all of 10 patients were negative for HBV DNA. Therefore the prevalence of occult HBV infection was 0 in studied patients with anti-HBc positive and anti-HBs negative.

DISCUSSION

The prevalence of occult HBV is unclear and varies significantly between different geographical regions. The world can be divided into three areas where the prevalence of chronic HBV infection is >8% (high endemicity), 2–8% (intermediate endemicity), and <2% (low endemicity). The sensitivity of the HBsAg and DNA assays used and the prevalence of HBV infection in the study population are important factor to clear the prevalence of occult HBV.[25,26] It is shown that the endemicity of HBV infection closely effect on the prevalence of occult HBV infection and patients are more likely to develop occult HBV infections in countries highly endemic for HBV and infrequently reported in low endemic areas.[27-29] At the present Iran is classified as having a low endemicity for HBV infection.[30] The present study showed that in studied HBsAg negative patients, the prevalence of anti-HBc positive was 20% but the rate of occult HBV infections was 0% in our study.

Table 1: Characteristics of studied patients

Variables	All patients (*n*=400)	Anti-HBc positive (*n*=32)	*P*
Age (years)	52.3±9.5	49.7±12.6	NS
Sex			
Female	166 (41.5)	17 (53)	NS
Male	234 (58.5)	15 (47)	
Duration of HD (month)	49.1±32.3	51.3±35.6	NS
Positive history of transfusion	288 (72)	27 (84)	NS
Tattooing	14 (3.5)	1 (3)	NS
History of renal transplantation	41 (10.2)	0	NS
History of diabetes mellitus	132 (33)	4 (12)	0.027

Data are mean±SD or number (%). *P* values calculated by *t*-test or Chi-square test. NS: Not significant, Anti-HBc: Antibody to hepatitis B core antigen, SD: Standard deviation, HD: Hemodialysis

Table 2: Frequency of various combinations of HBV markers

Anti-HBc	Anti-HBs	HBV DNA	Number (%)
Positive	Positive		22 (69)
Positive	Negative		10 (31)
Positive	Negative	Negative	10 (100)
Positive	Negative	Positive	0

Data are number (%). anti-HBc: Antibody to hepatitis B core antigen, Anti-HBs: Antibody to hepatitis B surface antigen, HBV: Hepatitis B virus

The prevalence of occult HBV infections reports ranges from 0% to 58% among patients in dialysis units in previous studies.[4,15-18] In a study by Ramezani *et al*.[24] of the 289 Iranian HD patients, 18 patients had isolated anti-HBc (6.2%), and the HBV-DNA was detectable in 50% of these patients (9 out of 18 patients). They reported the prevalence of occult HBV in these patients 3.1%. In a study by Gwak *et al*.[31] 65.8% were anti-HBc positive and the prevalence of occult HBV infection was reported as 0% in HD patients in Korea. In a large cohort of Italian chronic dialysis patients isolated anti-HBc was reported to be 20.8% of HD patients also they found that occult HBV was absent in their study group.[4] In Jardim *et al*. study the prevalence of occult HBV was 0% in 34 HD patients who were anti-HBc positive.[32] In a study involving subjects from Turkey, occult hepatitis B infection was found in 2.7% of HD patients.[21] In a survey in central Greece, the prevalence of occult HBV reported to be 0.9%.[33] In Motta *et al*. study[34] in 100 HBsAg negative HD patients the presence of HBV-DNA was detected in 15% of samples. In other studies, the prevalence of occult HBV reported to be in Spain 58%,[35] Canada 3.8%,[16] Italy 0%[4] and 26.6%,[20] Turkey 0%, 1.2%, 12.4% and 16.9%,[22,36-38] Egypt 4.1%[39] and in Brazil was reported to be 1.5%.[40] The higher prevalence of isolated anti-HBc is seen in endemic countries such as South-East Asia, sub-Saharan Africa and Greece and HBV-DNA is detected in about 10% of subjects with anti-HBc alone, with a range between 0% and 22.8%, depending on the geographical area and population selected.[41,42] Our results showed that in 400 HBsAg negative HD patients the presence of isolated anti-HBc was 8% and HBV-DNA was detected in 0% of these patients. As shown findings in present study is similar to some previous reports and also is dissimilar to some previous reports. These discrepancies in the rate of occult HBV infection in HD patients may reflect the diverse prevalence of HBV infection in different countries whereas Iran is classified as having a low endemicity for HBV infection and most of studies with similar results are done in countries with low endemicity of HBV infection and most of the high rates of occult HBV infection are shown in countries with

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high or intermediate endemicity of HBV infection. Other possible explanations of these discrepancies in the rate of occult HBV infection in HD patients include sensitivity of molecular biology techniques, size and virological features of the patient groups and the clinical specimens and specimen selection criteria for the HBVDNA tests. In our study the patients were selected for HBV-DNA assay if they had the positive anti-HBc result, and HBV DNA was not checked for anti HBc negative patients, this can be mention as the main limitation of the present study.

CONCLUSIONS

The prevalence of occult HBV infection in HBsAg negative patients undergoing HD at HD units was 0% and seems to be among the lowest worldwide. These results showed that occult HBV infection is not a significant health problem in HD patients in this region and quality of medical care and hygienic measures followed in HD units are appropriate for HD patients in Isfahan, Iran.

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Conflicts of interest
There are no conflicts of interest.

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