The Prevalence of HBV Infection in Renal Transplant Recipients and the Impact of Infection on Graft Survival

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Received: 14 Dec. 2018; Accepted: 28 May 2019

Abstract- Hepatitis B virus infection (HBV) is a leading cause of increased mortality and morbidity in renal transplant subjects. The purpose of this project was to investigate the prevalence of HBV in patients with renal transplant and compare it with the general population in Duhok city, Iraq. Then, the impact of HBV infection on graft function was evaluated. A total of 560 renal transplant subjects and 2975 volunteers were recruited in this study. All subjects were examined for HB surface antigen (HBsAg) positivity. Then, all HBsAg positive subjects were tested for viral load, alanine transaminase (ALT), aspartate aminotransferase (AST), serum creatinine and HBV profile. All HBsAg positive renal transplant subjects received treatment and were followed up for 24 months. It was found that 6/560 (1.1%) of the renal transplant subjects were HBsAg positive while 30/2975 (1.09%) of the volunteers were positive for HBsAg (P>0.05). After initiation of medications, viral load became undetected within 6 months of treatment. Serum creatinine levels were normal at the end of the study. No major side effects were recorded. The prevalence of HBV in renal transplant subjects was similar to the prevalence in general population. HBV infection did not show any negative effect on the graft function. Further study is needed with a larger sample size to explore the long term effect of the infection on graft functionality.

Acta Med Iran 2019;57(6):381-384.

Keywords: HBV; Renal transplant; Kidney transplant; Duhok; Iraq

Introduction

Infection with HBV is a public health problem that may predispose to deleterious consequences such as liver failure and hepatocellular carcinoma (1). It is estimated that approximately 400 million subjects are chronically infected with the virus (1). The prevalence of HBV differs from a country to another ranging from less than 1% in some Western countries to up to 10% in East Asia (1). In Iraq, the prevalence of HBV was studied previously, and it was ranging from around 1% in the northern region to 3.5% in the south (2-5). Renal transplant subjects are exposed to HBV infection risk factors in different stages and therefore; this group of patients is at high risk of the infection. The prevalence of HBV in subjects with renal transplant was studied previously, and it was found that it was as high as 20% in China (6). Recent studies in Portugal and Taiwan showed that the prevalence of the infection was 3% and 9%, respectively (6). Studying such an infection in such a group is crucial because HBV increases the mortality and morbidity in subjects with renal transplant (7). This might be due to immunosuppressive medications received after the operation may enhance the progress of fibrosis and worsen the outcome of HBV infection (7). The aims of this project were to compare the prevalence of HBV in renal transplant patient to the general population and to evaluate the effect of such an infection on graft outcome.

Materials and Methods

Viral markers

HBsAg and HBc-Ab IgG were tested by commercial

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LIAISON® XL diagnostic system (USA) per manufacturer's instruction. First, specific monoclonal antibodies (anti-HBs-Ag and anti-HBc-Ab) were fixed to the surface of microwells plates. Then, renal transplant recipients sera were added to the plate with the secondary conjugated monoclonal-antibody, conjugated with Horseradish Peroxidase (HRP). The reaction was blocked, and substrate was added. The optical density was measured by ELISA reader. HBeAg/Ab and HBc-IgM were tested by commercial DIA.PRO Diagnostic Bioprobes ELISA kit (Italy) as per manufacturer's instruction.

DNA extraction and RTPCR

DNA extraction was performed via QIAamp Viral DNA Extraction Kit (Qiagen, GmbH) per manufacturer instructions. RTPCR then was used to amplify and quantify HBV-DNA using artus® HBV RG PCR based real time PCR (Qiagen) as per manufacturer instructions. Reactions were analyzed by Rotor-Gene Q Real Time PCR.

Statistics

Data were introduced and analyzed utilizing Minitab 15 software. Descriptive statistics and percentage were employed. *Chi*-square test was used to study the significance in the differences, and P of ≤ 0.05 was considered significant.

Ethics

The study was approved by the Scientific and ethics committee, college of Medicine, University of Duhok. Written informed consent was obtained from all subjects before data collection.

Results

HBV positivity

A total of 560 renal transplant operations were performed during the period from 2009 to December 2015 with a male to female ratio of 2:1. The average age of transplant recipient was 34.3±12.6 years. We also examined 2975 volunteers from the public for HBsAg positivity. The average age of volunteers was 34.2±8.72 years. All renal transplant patients gave positive history for surgical procedures, blood transfusion, at least one session of renal dialysis and dental procedures. It was found that 6/560 (1.1%) of the renal transplant patients were HBsAg positive. On the other hand, 30/2975 (1.09) of the volunteers were HBsAg positive. No significant difference was found between renal transplant subjects and normal volunteers (*chi*-square, $P>0.05$).

HBsAg positive patients

To confirm the chronicity, all patients were examined for HBc-IgM and HBc-IgG. All HBsAg-positive subjects were negative for HBc-IgM and positive for HBc-IgG. All patients were examined also for HBe-Ag and HBe-AB positivity, and it was found that all patients were HBe-Ag negative HBe-AB positive. During our project, 6 subjects were diagnosed with chronic HBV. Three patients received tenofovir 300 mg while the rest were treated with entecavir 0.5mg. The patients were followed up for 24 months. Investigations including HBV viral load, liver enzymes including ALT and AST and serum creatinine were performed one month after the initiation of treatment and then every three months. Viral load test showed undetected levels in two patients one month after starting treatment. ALT and AST were normalized at the end of sixth month of treatment. The HBV viral load levels became undetected six months after starting treatment. At the end of the study, serum creatinine, ALT and AST levels were within the normal limits in all patients. No major side effect of anti-HBV was recorded.

Also, all patients were examined for viral load levels by a real-time polymerase chain reaction. The viral loads of two patients were negative (Table 1). Once the diagnosis was established, all patients start to receive anti-HBV medications (Table 1). The patients were followed up by RTPCR, liver function and serum creatinine (Table 1).

Table 1. Patient monitoring and selected laboratory values

		1 month				3 months				6 months			
Patients	**Drug**	ALT	AST	RTPCR	Ctn	ALT	AST	RTPCR	Ctn	ALT	AST	RTPCR	Ctn
Case 1	**Teno**	15	22	52 106	1.1	80	36	22344	1	40	22	undetected	1.2
Case 2	**Teno**	22	23	undetected	1.7	40	23	undetected	1.7	32	20	undetected	1.5
Case 3	**Ente**	44	20	334531	1	23	18	52000	0.97	22	23	undetected	1
Case 4	**Ente**	175	57	351000	1.2	84	33	undetected	1.5	53	29	undetected	0.9
Case 5	**Ente**	83	64	207909	1	65	31	814	1.2	24	19	undetected	1.5
Case 6	**Teno**	36	32	undetected	1.3	27	23	undetected	1.2	13	17	undetected	1.2
		12 months				**18 months**				**24 months**			
Patients	**Drug**	ALT	AST	RTPCR	Ctn	ALT	AST	RTPCR	Ctn	ALT	AST	RTPCR	Ctn
Case 1	**Teno**	46	45	undetected	1.1	28	42	undetected	1.1	22	17	undetected	1.2
Case 2	**Teno**	13	13	undetected	1.2	19	20	undetected	1.2	24	30	undetected	1.2
Case 3	**Ente**	22	17	undetected	1	14	19	undetected	1	15	15	undetected	1.2
Case 4	**Ente**	46	19	undetected	1	35	16	undetected	1	31	21	undetected	0.9
Case 5	**Ente**	15	14	undetected	1	16	16	undetected	1	22	20	undetected	1
Case 6	**Teno**	10	15	undetected	1.3	12	16	undetected	1.3	13	18	undetected	1.2

Abbreviations: ALT: Alanine transaminase; AST: aspartate aminotransferase; RTPCR: real time polymerase chain reaction; Ctn: creatinine; Teno: tenofovir; Ente: entecavir

Discussion

Infection with HBV is an important cause of morbidity and mortality in renal transplant patients (8). Therefore, early diagnosis and treatment of the infection in such a group of patients might decrease the complication and enhance life quality of renal transplant patients. In our study, we compared the prevalence of HBV in renal transplant recipients with the general populations. Previously, the effect of different infections on the outcome of renal transplant was studied in Iraq (9,10). In this study, we followed up renal transplant recipients with HBV infection for 24 months. It was noticed that within six months of treatment, the viral load of patients became undetected. At the end of the study, it was shown that the serum creatinine levels were within the normal limits. It seemed that HBV infection had no deleterious effect on the functionality of the graft. However, the duration of infection could not be determined in our subjects therefore; further research is needed to determine the long term influence of infection on graft functionality. Previously, a comparison was made in the five-year survival rates amongst HBs-Ag positive and HBsAg negative recipients. The five-year survival rates were the same in both groups (6). However, in another study, the ten-year survival rate was much higher in the HBsAg negative group than HBs-Ag positive group. In the same study, multivariate analysis revealed that HBV infection is an independent determinant of patient mortality and a leading cause of liver failure (11). Additionally, in another study, it was revealed that HBsAg positivity was an independent determinant for death after renal transplantation (12). Tenofovir and entecavir have been used for the treatment of HBV in renal transplant patients without major side effects (7). In support of this, in our study, these drugs seemed durable in decreasing the viral load, and no major side effect was recorded.

It was found previously that HBV might be reactivated after renal transplant. Also, it was shown that natural anti-HB surface antibodies might not protect against reactivation in such subjects (6). Therefore, periodic follow up was suggested to detect early reactivation in such patients (6). In our study, it was not clear whether those patients caught the infection before the transplant or after that. Examining patients' record revealed that the recipients were only examined for HBsAg. It is recommended that all recipients should be tested for HBsAg and HBc-Ab. It is also recommended that all recipients receive HBV immunization before the operation, if possible.

To conclude, the prevalence of HBV in kidney transplant subjects was similar to that of the general population. Our subjects were followed up for 24 months with anti-HBV medications. The infection did not show any negative effect upon the graft. Also, the medication used in our study appeared without major side effect. More studies are needed with a larger sample size with a longer duration to determine the effect of HBV infection and anti-HBV medications on graft survival.

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