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Research Article

Evaluation of hepatitis B vaccine responsiveness in hemodialysis and peritoneal dialysis patients

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ABSTRACT

Background: Hepatitis B Virus (HBV) infection is considered as a major cause of liver cirrhosis and hepatocellular carcinoma. Patients with End Stage Renal Disease (ESRD) are a risk group for HBV infection. The vaccine of hepatitis B has been recommended for prevention of HBV infection in ESRD patient especially on renal replacement therapy.
Methods: Eighty seven patients with ESRD on peritoneal dialysis and hemodialysis requiring primary hepatitis B vaccination were enrolled in the study. Each of them received 40 µg of recombinant hepatitis B vaccine in a four-dose schedule. Antibody response was determined by the levels of antibodies to the hepatitis B surface antigen (anti-HBs) after last doses of the vaccination schedule.
Results: We observed three response patterns to the immunizations in all patients after vaccination, the nonresponders (24.7%) never reached the minimum protective titer of 10 mIU/mL, the poor responders (18.5%) had titers between 10 and 100 mIU/mL, and the good responders (56.8%) had antibody titers above 100 mIU/mL. Despite a reduction in anti-HBs over time, the good responders did not become unprotected during the observation period, especially those participants who had titers above 1000 mIU/mL after the initial immunization.
Conclusions: We concluded that the immune response of the HBV vaccine was reduced in the HD and PD patients, which need yearly re-evaluation of seroconversion with booster doses of HBV vaccination if needed.

Keywords: End stage renal disease, Hepatitis B virus, Vaccine

INTRODUCTION

Hepatitis B Virus (HBV) infection is one of the widespread preventable infectious diseases. It considered as a major cause of liver cirrhosis and hepatocellular carcinoma. Patients with Chronic Kidney Disease (CKD) requiring Renal Replacement Therapy (RRT), essentially hemodialysis (HD), are already recognized as a risk group for HBV infection.[1]

The prevalence of HBV in HD patients varies significantly between countries, ranging from very low in developed countries to very high in some developing countries.[1]

HD patients are susceptible to infection with HBV resulting from blood transfusion, frequent injections, partial immunosuppression, or history of transplantation. Despite improvements in the prevention of HBV infection through national vaccination programs, implementation of compulsory and thorough blood donor

screening, and reduction of transfusion numbers due to erythropoietin administration, HBV infection still preserves its importance in HD centers.[2]

In the contrast, patients on Peritoneal Dialysis (PD) appear to have a low risk for HBV infection. But they should be vaccinated because it is likely that they will eventually need HD when PD becomes unfeasible, either temporarily or permanently.[3] Moreover, the peritoneal dialysate of patients positive for the Hepatitis B surface Antigen (HBsAg) contains sufficient infectious particles to cause hepatitis outbreaks in dialysis units.[4,5]

The vaccine of hepatitis B has been recommended for prevention of HBV infection in HD patients by Centers for Disease Control and Prevention (CDC) since 1982. The HBV vaccination is being used wide spreadly all around the world. While the percentage of the seroconversion is 90% in healthy individuals, it is only 50–70% in End-Stage Renal Disease (ESRD), especially in HD patients.[6-8]

Administration of Hepatitis B virus surface Antigen (HBsAg) in recombinant vaccines leads to the development of protective antibodies to HBV (anti-HBs) in responders. Lack of the development of anti-HBs means vaccines is susceptible to HBV infection.

In the present study, our objective was to identify the pattern of HB vaccination response of HD and peritoneal dialysis patients and when they become serologically negative for anti-HBs.

METHODS

Eighty-seven patients with ESRD on peritoneal dialysis and hemodialysis requiring primary hepatitis B vaccination were enrolled in the study over the period of September 2013 to August 2014 at Nephrology units, King Abdul Aziz Hospital, Jeddah, Saudi Arabia. During the study, there were 3 deaths from complications secondary to disease (Septic peritonitis and cardiovascular complications), two transfers to other facilities; one patient was referred for kidney transplants. So 58 HD and 23 PD patients were complete the follow up of 1 year.

All of them were serologically negative for hepatitis B surface antigen and antibody to hepatitis core antigen, and had not received hepatitis B vaccination in the past. 15 patients had a concomitant hepatitis C infection. Each of them received 40 µg of recombinant hepatitis B vaccine (Engerix-B®, GlaxoSmithKline, Belgium) given intramuscularly in the deltoid muscle in a four-dose schedule at 0, 1, 3, 6 months.

Immunogenicity or antibody response was determined by the levels of antibodies to the hepatitis B surface antigen (anti-HBs) at 1, 4, 8, 12 months after last doses of the vaccination schedule. Seroprotection was defined as achieving an anti-HBs level >10 IU/l after the fourth dose.

The subjects were grouped according to whether they developed seroprotective level of anti-HBs into 3 groups: non response group with low level of the antibody to hepatitis B surface antigen (anti-HBs <10 mIU/mL), a poor response group with anti-HBs level between 10-100 mIU/mL and good response group with anti-HBs level >100 mIU/mL. No booster dose was given in any patient of both groups during the follow-up period.

We recorded the details of all relevant clinical data and hepatitis antibody response during the follow-up.

All patients were examined for HbsAg, antibodies against hepatitis B core antigen (anti-HBc), anti-HBs, qualitative HBV DNR PCR and antibodies against HCV. All our patients have negative qualitative HBV DNR PCR. Antibody levels were determined using a commercial kit with enzyme immunoassay (Cobras Core Anti-HBs Quant EIA II; Roche Diagnostics GmbH, Mannheim, Germany).

We exclude patients chronically infected [surface antigen of HBV (HBsAg) positive] or anti-HBc positive, those co-infected with HIV, malignancy or hepatic failure, immunosupprive drugs, patients were unable to complete all four vaccinations and patients with previous history of poor response to HBV immunizations or whose vaccination knowledge was not enough or who were transferred to another center or got exit us during the following period.

The study was approved by the ethics committee of King Abdul Aziz hospital, conducted according to the declaration of Helsinki and written informed consent was obtained from each patient.

Statistical analysis

For the quantitative variables, the analysis was obtained by mean and standard deviation calculation. The evaluation of homogeneity between proportions of the qualitative variables was performed using the chi-square test or Fisher's exact test when there were expected frequencies less than five. For a three-group comparison, the two-way analysis of variance (ANOVA) was used by the Bonferroni test. The significance level applied for the tests was 0.05. The statistical package used in this study was SPSS, version 17.0, for Windows (IBM Corporation, Armonk, NY, USA).

RESULTS

The mean age of the 58, (22 males and 36 females), HD patients was 61 ± 13 years. They were in the hemodialysis program for approximately 49.25 ± 21.37 months. While the mean age of the 23 (10 males and 13 females) PD patients was 28.6 ± 16 years. They were at

the peritoneal dialysis programs for approximately 28.6 ± 16.2 months. According to the modality of dialysis, the response of seroconversion after hepatitis B vaccination, causes of renal failure, history of DM, the positivity of the anti-HCV and biochemical parameters are shown in Table 1.

The distribution ratio of response after hepatitis B vaccination in comparison of suspected risk factors are shown in Table 2. The percentage of the anti-HBs among HD and PD patients was 86.2% and 82.6 % respectively after one month of follow up with a reduction of the percentage of seroconversion in both groups during follow period as shown in Table 3.

Table 1: Demographic, clinical and laboratory characteristics of patients enrolled in the study.

Variable	HD (no: 58)	PD (no: 23)	P value
Age	61.2 ± 13.5	55.6 ± 20.3	0.23
Gender M/F	22/36	10/13	0.65
Duration on dialysis (month)	49.25 ± 21.73	28.61 ± 16.24	0.00002
Causes of renal failure			
-Hypertensive nephropathy	17	10	
-Diabetic nephropathy	14	7	
-Chronic glomerulonephritis	7	2	
-Obstructive uropathy	2	0	
-Polycystic kidney disease	2	0	
-Unknown	16	4	
BMI (kg/m$^{2)}$	26.1 ± 4.82	24.6 ± 3.72	0.14
DM	18	11	0.16
Urea (mg/dl)	74.5 ± 36.1	87 ± 20.54	0.05
S. creatinine (mg/dl)	6.5 ± 3.75	7.21 ± 2.95	0.37
S. albumin (g/dl)	3.9 ± 0.98	3.41 ± 0.81	0.03
Hemoglobin (g/dl)	9.84 ± 1.65	10.53 ± 1.09	0.03
ALT (U/ml)	22.4 ± 12.7	25.8 ± 8.2	0.16
HCV Ab (positivity No.)	13 (22.41%)	2 (8.7%)	0.21
HBV seroconversion rate at 1 month post vaccine	50 (86.2%)	19 (82.6%)	0.95

Table 2: Comparison between seroconversion and nonseroconversion group at the end of 1 year follow up.

Variable	Non response <10 mIU/mL, No. 20 (24.7%)	Poor response 10-100 mIU/mL, No. 15 (18.5%)	Good response >100 mIU/mL, No. 46 (65.8%)	P value
Age (year)	53 ± 9	56 ± 12	52 ± 13	0.206
Gender M/F	8/12	10/5	18/28	0.158
BMI (kg/m^2)	25.7 ± 5.3	24.9 ± 3.8	25 ± 4.1	0.299
DM (No.)	8	7	13	0.360
HCV Ab (positivity, No.)	5	2	8	0.649
Albumin (g/dl)	3.5 ± 1.08	4.11 ± 0.8	3.7 ± 0.85	0.272
Dialysis modality (H/P)	14/6	9/6	35/11	0.478
ALT (IU/l)	24.3 ± 7.8	21.5 ± 5.1	18.9 ± 11.6	0.123
Duration on dialysis (month.)	45.5 ± 18.3	39.7 ± 21	35 ± 16.5	0.509

Table 3: Follow up HBV seroconversion.

	HD (no: 58) (%)		PD (no: 23) (%)	
	No response	Seroconversion	No response	Seroconversion
1 (month)	8 (13.8)	50 (86.2)	4 (17.4)	19 (82.6)
4 (month)	9 (15.5)	39 (84.5)	4 (17.4)	19 (82.6)
8 (month)	10 (17.2)	48 (82.8)	6 (26.1)	17 (73.9)
12 (month)	14 (24.2)	44 (75.8)	6 (26.1)	17 (73.1)

DISCUSSION

Hepatitis B Virus (HBV) infection in high risk population poses a serious risk to their life with the development of lifelong infection, cirrhosis (scarring) of the liver, liver cancer, liver failure, and death.

Patients with CKD requiring RRT, essentially HD, are at increased risk for HBV infection because of the opportunity for exposure to HBV associated with the dialysis procedure. Therefore, the hepatitis B vaccine is the mainstay of hepatitis B prevention in high risk population like patients on chronic dialysis therapy.

We observed three response patterns to the immunizations in all patients after 4 doses of HBV vaccination, the nonresponders (24.7%) never reached the minimum protective titer of 10 mIU/mL, the poor responders (18.5%) had titers between 10 and 100 mIU/mL, and the good responders (56.8%) had antibody titers above 100 mIU/mL. We found that despite a reduction in anti-HBs over time, the good responders did not become unprotected during the observation period, especially those participants who had titers above 1000 mIU/mL after the initial immunization.

The immunization response of patients enrolled in the study is nearer to previous study's results. Lin et al. found that an HB response vaccination rate of 70.5% in 156 dialysis patients.[9] while Pin et al. found that only 67.8% of HD patients remained immune after a 1-year follow-up and 16% of subjects were already susceptible prior to their 6-month follow-up.[10]

The reduction in antibody response against vaccine in the follow up period for our patients might be related to several causal factors that belong to cell-mediated immunity as impairment of the monocyte function, reducing T-cell proliferation and insufficient IL-2 production, are the essential factors.[11,12]

The most obvious finding to emerge from the analysis is that there is non-significant differences have been found in the rates of seroconversion between patients on peritoneal dialysis and those on hemodialysis, which agree with study has been done by Hoofnagle et al.[13]

The results of this study show that there were no statistically significant differences in the response to the vaccination in terms of age, sex, presence of diabetes comorbidity, duration of dialysis and the presence of HCV coinfection. In addition, no difference in response regarding their nutritional status (serum albumin and BMI as markers of nutritional status). In contrast to a previous study by Kara et al who observed that The insufficient immune response was higher (87.5%) among the HD patients who had albumin levels between 3 and 3.5 g/dL, but the insufficient immune response was extremely low (18.8%) among the HD patients who had albumin levels between 4.5 g/dL and more than 4.5 g/dL.[14]

These results are consistent with the data observed in previous similar studies that was also suggested that there was no relation between response rate against HBV vaccine and age, gender, HD time, anti-HCV positivity, and the number of the vaccination doses in the similar studies.[15-20]

There are also some limitations that should be pointed out. First, the relatively short study period, although we evaluate the dialysis patients during 1 year follow up after vaccination, we expect that vaccinated patients will lose the protective anti-HBs titers (≥10 mIU/ml) during long term follow up, so we suggest that yearly re-evaluate is necessary. Second, it is possible that larger sample size would have produced more significant findings.

In the conclusion, it was realized that the immune response of the HBV vaccine was reduced in the HD and PD patients, which need yearly re-evaluation of seroconversion with booster doses of HBV vaccination if needed.

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