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Original Article

Response Rate to Hepatitis B Vaccination in Patients with Chronic Renal Failure and End-Stage-Renal-Disease: Influence of Diabetes Mellitus

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ABSTRACT

Background: Hepatitis B vaccination is recommended for all individuals with renal failure. Nevertheless, the response rate for this vaccine in hemodialysis patients is low. This study was designed to determine the response rate to hepatitis B vaccination in chronic renal failure (CRF) and end stage renal disease (ESRD) patients and those factors that influence it.

Methods: We evaluated antiHBs level after primary vaccination in 32 predialysis and 93 dialysis patients. HBsAg positive patients were excluded. AntiHBs titers were determined in the period of 1 to 6 months after completion of vaccination.

Results: Seroconversion (antiHBs≥10mIU/ml) was found in 100 patients (80%), but an excellent response (titer>100 mIU/ml) was observed only in 74 (59.2%). Response rate were 71.9 and 82.8 in predialysis CRF and ESRD patients, respectively, but this difference was not significant (χ^2-test; p=0.183). Predialysis patients showed an excellent response more than dialysis patients (χ^2-test; p<0.05). Age, sex, and initial serum creatinine didn't influence response rate. Response rate in patients with diabetic mellitus was lower than others (62.2% vs. 87.5%) (χ^2-test; p=0.001), and multiple logistic regression analysis showed a significant risk for vaccination nonresponse when patients were diabetics (odds ratio 4.38; 95% confidence interval: 1.70-11.24, p=0.002).

Conclusion: Our result showed that 1) hepatitis B vaccine nonresponders are more likely to have diabetes mellitus and 2) response rate in predialysis patients is the same as in dialysis patients but predialysis patients, as compared with dialysis patients, were more inclined to show an excellent response.

Key words: HBV vaccination, Chronic Renal Failure, dialysis, Diabetes Mellitus

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Hepatitis B virus (HBV) infection has been a major threat to patients treated with long-term hemodialysis (HD). These patients are at risk of acquiring hepatitis B infection during hemodialysis session and subsequently becoming chronically infected with the virus [1]. Hepatitis B vaccines are effective in providing protection against this infection [2], but patients with end stage renal disease (ESRD) have a reduced response to vaccination because of the general suppression of the immune system associated with uremia. Compared to vaccination in normal individuals, dialysis patients have a lower antibody titer and an inability to maintain adequate antibody titers over time [3].

In Iran, it is the guideline for hepatitis B vaccination of patients with ESRD to be administrated hepatitis B vaccine on schedule of 0-1-6 months with double-dose of HBV vaccine (40μg). This study was designed to determine the response rate to HBV vaccination in

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chronic renal failure (CRF) and ESRD patients vaccinated on this method. In addition, patient factors that influence response to HBV vaccination were examined at the start of vaccination for CRF and ESRD patients in a patient population, representative of dialysis and predialysis CRF population in Isfahan.

Subjects and Methods

In this longitudinal prospective study the cases were collected from Noor and AL-Zahra dialysis centers (Isfahan University of Medical Sciences), and Isfahan nephrology clinics. The sampling was performed by simple method and involved all patients who got the entry criteria to the study in period of 12-monthes. Entry criteria to the study included patients with CRF (Serum Creatinine>2 mg/dL for more than three months) or ESRD whom was vaccinated against hepatitis B on schedule of 0-1-6 months with double-dose (40μg) of hepatitis vaccine. Subjects who 1) were HBs-antigen or HBs-antibody positive (before beginning of the vaccination), 2) have not been vaccinated regularly, and 3) were not checked for antiHBs during 1-6 months after the last dose of vaccination, were excluded in the analyses.

The vaccine used in this study was Heberbiovac HB (Heber Biotec. S.A P.O. Havana), hepatitis B recombinant vaccine which contains a preparation of the surface antigen of the hepatitis B virus obtained from cultures of the transformed yeast. Each 1 ml of this vaccine contains 20μg of 95% HBsAg. This vaccine was administered to all patients with dose of 40μg as intramuscular deltoid injections on a schedule of 0, 1, and 6 months. Patients, who received all 3 doses of their vaccines before entry to chronic dialysis stage, were considered as predialysis CRF patients group and those who received one of their doses of vaccines in chronic dialysis stage were considered as dialysis ESRD patients group.

Before beginning of the vaccination, HBsAg, HCV-Ab, HBs-Ab and HIV-Ab were checked in all patients. All demographic data were collected in questionnaires prepared for this purpose. Antibodies to hepatitis B surface antigen (antiHBs) were determined approximately 1 to 6 months after completion of initial vaccination series to assess response to vaccination (by the ELISA technique, with kits created in Behring Co.). These examinations were performed in Isfahan Blood Transfusion Center. A subject had responded to the vaccine if the antiHBs level was ≥10mIU/ml. Those with levels 10–100 mIU/ml were termed 'adequate responders', whereas those with levels >100 mIU/mL were termed 'excellent responders'.

Statistical analysis included t-test and chi-square test for comparison between groups. A logistic regression model was used to identify predictors of seroconversion.

Results

Of 125 patients entered this study, 93 patients were on hemodialysis and 32 patients were chronic renal failure cases in predialysis stage. The patients' characteristics are summarized in table 1.

100 patients (80%) responded to vaccination, and 74 patients (59.2%) showed an excellent response. Of 93 dialysis patients, 77(82.7%) responded to vaccination, and 53(57%) showed an excellent response. In predialysis patients, 23 of them (71.9%) responded to vaccination and 21 (65.6%) showed an excellent response (Figure 1). Despite response rate in dialysis patients were higher than predialysis ones, but there wasn't any significant difference between them (χ^2-test; p=0.183). Although, no significant overall response to vaccination was seen in dialysis and predialysis patients, but there was a significant higher excellent response to vaccination in predialysis patients (χ^2-test; p<0.05).

Of 6 patients that used immunosuppression and glucocorticoids with together (in the period of 1 year before beginning of vaccination or in vaccination period), 2 patients did not respond to vaccination. Both of these nonresponder patients used Prednisolone and Azathioprine in vaccination period. Other four who responded, used Prednisolone and Cyclophosphamide and only one of them used

these drugs in vaccination period. Of 2 patients that

Table 1. Characteristics of dialysis, predialysis and total patients.

Characters	Dialysis Patients (n=93)	Predialysis patients (n=32)	Total patients (n=125)
Mean Age (years ± SD)	48.18± (17.13)	55.28± (13.80)	50.01± (16.58)
Male (%)	63 (67.7%)	14 (43.7%)	77 (61.6%)
Cause of Renal Failure			
Diabetes mellitus	27 (29.0%)	10 (31.2%)	37 (29.6%)
Hypertension	22 (23.6%)	5 (15.6%)	27 (21.6%)
Glomerulonephritis	5 (5.4%)	3 (9.4%)	8 (6.4%)
Interstitial Nephritis	12 (12.9%)	3 (9.4%)	15 (12%)
Poly-cystic Kidney Disease	4 (4.3%)	3 (9.4%)	7 (5.6%)
Unknown and etc.	23 (24.7%)	8 (25.0%)	31 (24.8%)
Serum Creatinine (at the beginning of vaccination) ± (SD)	-	3.12 ± (0.84)	-

SD: Standard Deviation

used only Prednisolone in vaccination period, both responded to vaccination. Two patients were HCV-Ab positive and no patient was HIV-Ab positive. Both HCV-Ab positive patients were excellent responders. In table 2, baseline patients' data at the start of vaccination is summarized in responder and nonresponder groups. Although, there was a trend to better response in younger patients, it was not statistically different from the nonresponders values (t-test; p=0.167).

Demographic data analysis in responders and nonresponders revealed trends toward gender based differences. The female patients had trend toward better antibody response than male patients, but this difference did not reach statistical significance (χ^2-test; p=0.462) (Table 2).

In addition, Initial mean serum creatinine in predialysis responder patients was lower than nonresponder's (Table 2), but there was not a significant association between initial serum creatinine level and response rate (t-test; p=0.606)

Among different causes of renal failure, response rate in diabetic patients was lower than other causes of renal failure. Only 23 (62.2%) patients from 37 patients with diabetes mellitus responded to vaccination, while, of 88 patients with other causes of renal failure, 77(87.5%) responded to vaccination and chi-square test showed a significant difference between them (χ^2-test; p=0.001).

Table 2. Characteristics of patients in responder and nonresponder groups.

Characters	Responder (n=100)	Nonresponder (n=25)
Mean Age (years ± SD) @	48.98± (14.44)	54.12 ± (16.98)
Sex (F/M)*	40/60	8/17
Cause of Renal Failure		
Diabetes mellitus	23 (62.1%)	14 (37.8%)**
Hypertension	24 (88.8%)	3 (11.1%)
Glomerulonephritis	7 (87.5%)	1 (12.5%)
Interstitial Nephritis	13 (86.6%)	2 (13.3%)
PCK	5 (71.4%)	2 (28.5%)
Idiopathic and etc.	28 (90.3%)	3 (9.6%)
Serum creatinine	3.07+/-(0.78)	3.25+/-(1.04)#

SD: Standard Deviation, Responder: antiHBs≥ 10mIU/mL, PCK: Poly-cystic Kidney Disease
@: p=0.167;t-test
*: p = 0.462; chi-square
**: p=0.001 v others; chi-square
#: p=0.606; t-test. (only in predialysis patients)

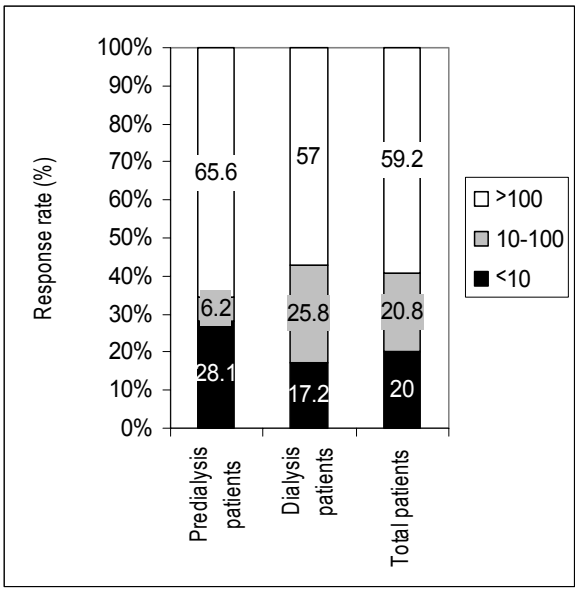

Figure 1. Relative frequency of excellent response, adequate response, and nonresponse in dialysis, predialysis, and total patients.

Adequate vs. excellent response is ahown in predialysis and dialysis patients (p< 0.05).

Multiple logistic regression analysis examining age, dialysis treatment, presence of diabetes mellitus and male sex showed a significant risk for vaccination nonresponse when patients were diabetics (odds ratio 4.38; 95% confidence interval: 1.70-11.24) (table 3). There was no association between age>60 years, male sex, and presence of dialysis with response rate.

Table 3. Multiple logistic regression model for failure to seroconvert after hepatitis vaccination.

Predictor variable in model	*Odds ratio*	Confidence Interval	p-value
Presence of DM	4.38	1.70-11.24	0.002
Age>60 years	1.96	0.74-5.21	0.175
Male	1.67	0.60-4.36	0.325
Dialysis	0.47	0.17-1.33	0.154

Likelihood ratio test statistic: 35.862 P<0.0005
DM: diabetes mellitus

Discussion

Patients with ESRD have a reduced response to vaccination because of the general suppression of the immune system associated with uremia, compared to vaccination in normal individuals. For example, dialysis patients have a lower antibody titer and an inability to maintain adequate antibody titers over time [3].

Patients with CRF suffer from defective host defenses, which are directly the result of the renal impairment, in addition to those dependent on the primary illness leading to the renal failure [4].

The CRF and ESRD patients in this study showed a response rate of 80% to HBV vaccination, which is in the upper limit of vaccination response rate in the prior studies which has been performed on this subject (ranges: 34%-76.7%) [5, 6]. Another point to pay attention to, is that this good response rate (80%) doesn't mean that these dialyses centers are safe from HBV outbreaks. National surveillance data have demonstrated that independent risk factors among chronic hemodialysis patients for acquiring HBV infection include the present of one or more HBV infected patient in the hemodialysis center who is not isolated, as well as a less than 50% hepatitis B vaccination rate among patients [7]. Therefore, segregation of the HBsAg positive patients, universal precautions, and vaccination of the patients should be kept observed carefully.

Among persons with normal immune status who respond to the primary series of hepatitis B vaccine, protection against hepatitis B persists even when antibody titers become undetectable. However, among hemodialysis patients who respond to the vaccine, protection against hepatitis B is not maintained when antiHBs titers fall below 10mIU/ml [8]. Navarro et al, in 1996 showed that after hepatitis B vaccination, an antibody titer higher than 100mIU/ml is necessary to maintain the antibody level 1 year later [6]. In this study, it was shown that 59.2 percent of patients could ac-

quire an antibody titer higher than 100mIU/ml. In prior studies, 31-53.5 percent of patients showed an antibody titer higher than 100 [6, 9].

The relative antibody response to a vaccine also appears to correlate with the degree of renal failure, but not with the specific mode of dialysis. Some studies have demonstrated that higher antibody response rates can be achieved by vaccinating patients with chronic renal failure before they become dialysis dependant, particularly patients with mild to moderate renal failure. In the largest of these studies conducted by Agarwal et al, a significant difference in seroconversion was shown between patients with mild (creatinine level, 1.5-3 mg/dl) and severe (creatinine level >6 mg/dl) renal failure (87.5% in mild versus 35.7% in severe CRF) [10]. But in earlier studies, a lower response to recombinant vaccine was reported among predialysis patients, possibly because patients with more severe renal failure were included [11, 12]. It is not clear at the current time whether level of kidney dysfunction is an independent predictor of seroconversion or level of chronic renal failure serves as a marker for other factors, such as malnutrition and anemia that can have an impact on the immune response. Gerald Darosa et al, showed, that patients with higher GFR level are more likely to response to hepatitis B vaccination programs with seroconversion, independent to other factors [13]. In our study, the dialysis patients showed a response rate higher than predialysis patients, however, there wasn't any significant difference between them. However, predialysis patients showed a statistically better antibody response of more than 100mIU/ml comparing with HD patients. Therefore, we recommend starting vaccination program in chronic renal failure patients in early stages of disease to achieve more effective antibody response and to protect HD patients in the first 6 months of their dialysis program.

In the prior studies, age was the major determinant of vaccine response. Ramon et al showed that 100% of patients with age less than 40 years old responded to vaccine versus 74% of patients with age more than 60 years old [14]. Older age in the hemodialysis population has been routinely associated with a poorer vaccination response [14, 15, 16, 17], despite that some studies didn't show a significant association between age and response rate [10, 18]. The findings of this study showed that vaccine responders were younger than nonresponders (48.98 years old in responders versus 54.12 years old in nonresponders). Although, there was a trend to response in younger patients, it was not statically different from the value in nonresponders. How ever, we suggest that a higher-powered study may find these parameters statistically significant.

Other host factors that contribute to decreased immunogenicity include smoking, and male sex [6, 7, 19, 20]. Some studies only showed a greater percentage of men in the nonresponding group and other studies showed this for female sex [14, 19]. In our study, the females responded better to vaccination but there wasn't any significant association between them.

Limited data indicate that concurrent infection with HCV does not interfere with development of protective levels of antibody after vaccination, although lower titers of antiHBs have been reported after vaccination of HCV positive patients compared with HCV negative patients [21, 22], but Navarro et al in 1996 showed that HCV infection might reduce the effectiveness of hepatitis B vaccine in hemodialysis patients [6]. In this study both HCV-Ab positive patients responded to vaccination.

Some studies did not show a significant association between presence of diabetes mellitus (DM) in HD patients and poor response rate [23, 24], but Andrew I Chin, in 2003, showed a significant association between DM and low response rate and suggested that DM has an independent association with a poor vaccination response rate (odds ratio: 3.4, P=0.014) [17]. The literature regarding HBV vaccination in non-renal failure DM subjects suggests a decreased vaccination response rate compared with healthy controls [25, 26]. Diabetics appear to have a lower degree of antigen presentation

and T-cell function [27]. Besides some decreased cellular responses in vitro, no disturbances in adaptive immunity in diabetic patients have been described. Different disturbances (low complement IV factor, decreased cytokine response after stimulation) in humoral innate immunity have been described in diabetic patients. However, the clinical relevance of these findings is not clear. Concerning cellular innate immunity, most studies have shown decreased functions (chemotaxis, phagocytosis, killing) of diabetic polymorphonuclear cells and diabetic monocytes/ macrophages compared to cells of controls. In general, a better management of the DM leads to an improvement in these cellular functions [28]. The findings in this study also showed a significant association between presence of DM and low response rate in CRF and ESRD patients (P=0.001). Also, the parameters used in the multiple regression model suggested that DM has an independent association with a poor vaccination response rate (odds ratio: 4.34, P=0.002).

In conclusion, this study showed that 1) there is a good response rate to hepatitis B vaccination in CRF and ESRD patients in our centers compared with prior studies, 2) hepatitis B vaccine nonresponders with CRF or ESRD are more likely to have diabetes mellitus and 3) response rate in predialysis CRF patients is the same as the dialysis patients but predialysis CRF patients as compared with dialysis patients are more inclined to show an antibody response higher than 100 mIU/ml.

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