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REVIEW

Is hemodialysis a reason for unresponsiveness to hepatitis B vaccine? Hepatitis B virus and dialysis therapy

Dede Sit, Bennur Esen, Ahmet Engin Atay, Hasan Kayabaşı

Dede Sit, Bennur Esen, Ahmet Engin Atay, Hasan Kayabaşı, Department of Internal Medicine and Nephrology, Bagcilar Education and Research Hospital, Istanbul 34200, Turkey

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Correspondence to: Dede Sit, Associate Professor, Department of Internal Medicine and Nephrology, Bagcilar Education and Research Hospital, Mimar Sinan Avenue, 6. Street, Bagcilar, Istanbul 34200, Turkey. drdede75@hotmail.com
Telephone: +90-532-6462297

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Abstract

Impaired renal function is associated with a high risk of chronicity of hepatitis B virus (HBV) infection. Patients on hemodialysis (HD) or peritoneal dialysis are at an increased risk of viral transmission due to frequent necessity of blood product transfer as well as use of contaminated dialysate or dialysis materials. Additionally, health professionals may cause viral spread *via* contaminated hands and carelessness against hygiene rules. The frequency of chronic HBV infection may be as high as 80% in patients on renal replacement therapies. This is because HBV vaccination is essential to eliminate chronic HBV infection. However, response rates of HD patients to HBV vaccination vary between 10%-50%. Dialysis adequacy and early vaccination before the onset of dialysis therapy seem to be major determinants of high seroconversion rates. Older age, male gender, duration of dialysis therapy and nutritional status are other well-known factors associated with seroconversion rate. There are controversial reports regarding the role of the presence of diabetes mellitus, HCV positivity, erythropoietin resistance, hyperparathyroidism, and vitamin D inadequacy. The role of genetic alteration in the functions or production of cytokines still needs to be elucidated.

Key words: Hepatitis B virus; Vaccine; Hemodialysis; Response; End stage renal disease

Core tip: Due to immunesuppresive effect of uremia and dialyser membranes, chronicity of hepatitis B virus (HBV) infection is frequently observed. Rates of seroconversion induced by HBV vaccine is diminished in chronic kidney disease patients when compared to the general population, which gradually decrease as renal functions deteriorates. Efficient dialysis is a major determinant of response to HBV vaccination. In contrast to three doses of 20 μg HBV vaccine for the general population, patients on hemodialysis or peritoneal dialysis usually require four doses of 40 μg HBV vaccine.

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INTRODUCTION

Hepatitis B virus (HBV) infection is an important public health problem affecting approximately 500 million people worldwide[1-3]. According to 2010 data, 360 million people have chronic HBV infection that leads to more than 1 million deaths/year due to acute hepatitis, cirrhosis or hepatocellular carcinoma[4,5].

Patients with chronic kidney disease (CKD) exhibit an impaired immune response against host agents including HBV due to bone marrow suppression caused by uremia and loss of CD4 T cells by use of bio-incompatible dialysate and membranes[6,7]. Patients on hemodialysis (HD) or peritoneal dialysis (PD) have an increased risk of HBV related complications. On the other hand, the rates of seroconversion induced by HBV vaccination in patients with CKD is significantly lower than those in the general population[8,9].

THE EPIDEMIOLOGY OF HBV INFECTION

Chronic HBV infection is associated with high morbidity and mortality by leading to carrier state or chronic infection[10-14]. Pediatric population, especially newborns, as well as individuals at an advanced age are at an increased risk of chronicity of HBV infection[15]. Clinical course of chronic HBV infection may vary from asymptomatic carrier state to cirrhosis or even hepatocellular carcinoma[16].

Recently, the rates of hepatitis B surface antigen (HBsAg) positivity is 0.1% in Western countries[17]. However, it is significantly higher in some areas like southeastern Asia and Middle East. The majority of southeast Asia and Middle East countries have an intermediate or high endemicity of HBV infection[18]. Based on the data in 2009, the rate of HBsAg positivity was 4.4% in the Turkish population (ranging from 2.5% to 9.1%)[19]. Figure 1 shows the geographic distribution of chronic HBV infection.

THE RISK OF CHRONICITY IN THE GENERAL POPULATION AND DIALYSIS PATIENTS

The chronicity rate of HBV infection is 5%-10% in the general population, whereas it may be as high as 60%-80% in patients receiving renal replacement therapy (RRT)[20]. Nucleoside analogues and interferon (IFN) are choices of treatment; however, a sustained viral response is achieved in only 30%-40% of patients on dialysis[21]. Owing to the fact that the chronicity rate of HBV infection is high and success rate of antiviral therapy is low in dialysis population, preventive measures against HBV infection is of vital importance.

Since the first recommendation of HBV vaccination by the Center for Disease Control and Prevention, the United States in 1982, administration of recombinant HBV vaccine which is composed of HBsAg is routinely used[22].

ADMINISTRATIONS OF HEPATITIS B VACCINE

Former vaccines were derived from human plasma; however, as a consequence of innovations in vaccine technology, vaccines produced by recombinant DNA technology were introduced[23]. Recombinant HBV vaccine composed of HBsAg is associated with high seroconversion rates[24]. Recombinant HBV vaccine contains 20 μg HBsAg solution and 0.5 mg aluminium salt[25]. A number of adjuvants including levamisole, zinc, interferon, interleukin-2 (IL-2) and thymopoietin were added to increase the effectiveness[26-32].

Neutralizing antibodies against HBsAg indicate prior infection with HBV or triggered immune response against HBsAg in HBV vaccination[33-37]. Exposure to HBV is defined as appearance of HBsAg with or without antibody to hepatitis B e antigen (HBeAg) and hepatitis B core antigen (HBcAg)[38]. A group of patients may be in the window period which is associated with sole appearance of IgM class antibody against HBcAg[39]. Seroconversion of HBV is defined as appearance of antibodies to HBsAg (antiHBs) in the absence of HBsAg, HBeAg, HBcAg and undetectable HBV DNA[40]. Table 1 summarizes the interpretation of serologic results.

HBV vaccination should be started before the initiation of RRT[41]. Currently, intramuscular administration HBV vaccine at 0, 1, 2 and 6 mo at a dose of 40 μg is recommended. Instead of gluteal region which contains muscle and fat, deltoid muscle is a preferable area to increase response rates[42].

There are variable response rates to HBV vaccination among HD patients. Inadequate seroconversion rates in the general population and patients on RRT are 5%-10% and 40%-50%, respectively[43]. According to another report, 20% of vaccinated patients on HD still does not achieve antibody formation against HBsAg[44].

Lack of consensus exists regarding determining optimal vaccination schedule for patients with CKD at predialysis stage. For patients on RRT, the recommended vaccination schedule contains twice the dose of the general population (40 μg) in 4 cycles at intervals of 0, 1, 2 and 6 mo administered by intramuscular route at one site[45]. Additional three cycles of HBV vaccine should be administered to patients who do not respond to primary schedule[46,47] (Figure 2).

THE RATES OF RESPONSIVENESS AND NONRESIVENESS TO HBV VACCINATION IN DIALYSIS PATIENTS

Because patients on RRT have blunted immune response, they exhibited an unsatisfactory response to HBV vaccination when compared to healthy individuals[48]. Dacko *et al*[49] concluded that efficient

Table 1 Interpretation of serologic markers of hepatitis B virus

HBsAg	Total anti HBc	IgM anti HBc	AntiHBs	Interpretation
-	-	-	-	Noninfected
+	-	-	-	Acute infection (early phase)
+	+	+	-	Acute infection
-	+	+	-	Recovering acute infection
-	+	-	+	İmmunized patient, past infection
+	+	-	-	Chronic infection
-	+	-	-	Chronic infection with low level viremia or false positive
-	-	-	+	Immunized

HBsAg: Hepatitis B virus surface antigen; antiHBs: Antibodies to HBsAg.

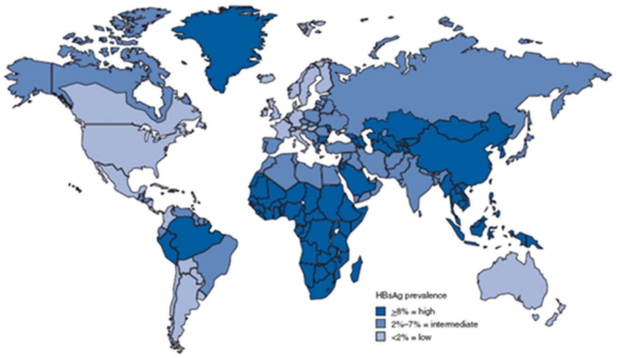

Figure 1 Distribution of chronic hepatitis B virus infection (From Weinbaum *et al*[96]).

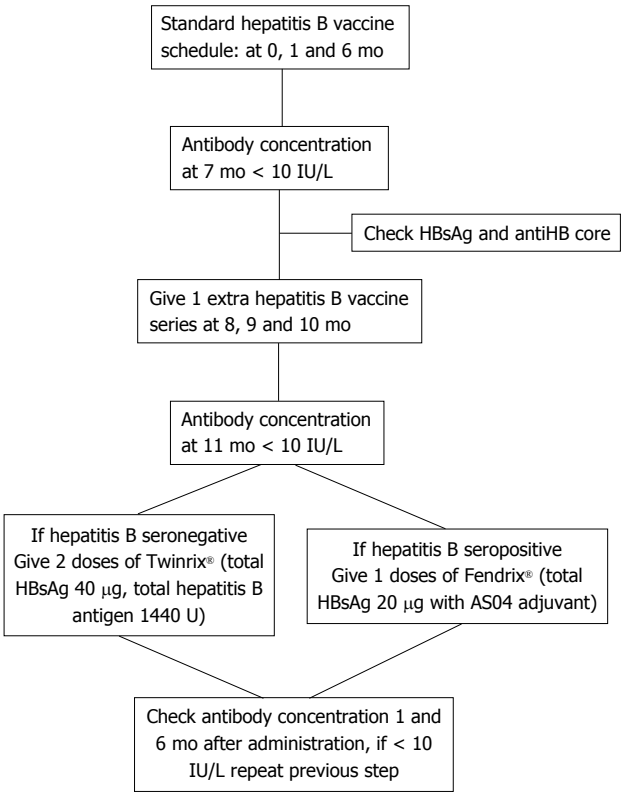

Figure 2 Schedule of hepatitis B vaccine (Schillie *et al*[97]). HBsAg: Hepatitis B virus surface antigen; antiHB: Antibodies to HBsAg.

hemodialysis, age, nutritional status and systemic inflammation are determinants of an adequate response to HBV vaccination[49]. Similarly, Hashemi *et al*[50] stated that duration of dialysis, hemoglobin, and parathyroid hormone level and accompanying HCV infection do not affect immune response to HBV vaccination[50].

Seroconversion and adequate response are defined as anti-HBs > 10 IU/mL and > 100 IU/mL, respectively. Buti *et al*[51] stated that seroconversion was achieved in 76.7% of HD patients whereas adequate response was observed only in 53.5% at the third month of vaccination[51]. In a report from Saudia Arabia, adequate response rates reached 89.5% in HD patients[52]. Similarly, some reports determined satisfactory seroconversion rates among HD patients. Jadoul *et al*[53] showed that the seroconversion rate among HD patients was 89.65%[53]. A suboptimal response to HBV vaccine in HD patients is probably related to immunologic factors and poor nutritional status. Patients on RRT have impaired humoral and cellular immune response leading to underproduction of antibody.

Seroconversion rates may vary in different stages of CKD. Agarwal *et al*[47] performed a study to determine response rates to HBV vaccine in mild (creatinine 1.5 mg/dL to 3.0 mg/dL), moderate (creatinine 3.0 mg/dL to 6.0 mg/dL) and severe (creatinine > 6.0 mg/dL) CKD[47]. They pointed that seroconversion rates by three doses of 20 μg HBV vaccine in mild, moderate and severe CKD were 87.5%, 66.6% and 35.7%, respectively, which were significantly lower than seroconversion rates achieved by four doses of 40 μg (100%, 77% and 36.4%, respectively).

There are some reports with regard to the role of administration route on the rate of serconversion in HD patients. In a meta-analysis including 14 studies and 718 adult patients on HD, Fabrizi *et al*[54] concluded that seroconversion rate associated with intramuscular administration of HBV vaccine is significantly lower than that with intradermal administration [odds ratio (OR) = 0.454, 95%CI: 0.30-0.67, P = 0.001)[54].

There are controversial reports regarding success rate of HBV vaccination in patients at predialysis stage and patients on dialysis therapy. Taheri *et al*[55] indicated that response rate to HBV vaccination in predialysis patients is similar to that in dialysis patients. In contrast, Seaworth *et al*[56] observed that patients at predialysis

stage have a more favorable outcome than patients at dialysis stage, suggesting that vaccination should be given as early as possible.

In conclusion, several factors including advanced age, DR3, DR7 and DQ2 positivity and the absence of A2 alleles may influence a response to hepatitis B vaccine in HD patients. Natural HBV infection achieves higher seroconversion rates than HBV vaccination; however, current HBV vaccination schedule provides remarkable seroconversion rates.

PATHOGENESIS OF UNRESPONSIVENESS TO HBV VACCINATION

HBV vaccination stimulates specific antibody production by the activation of B cells, which is mediated by $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells[57]. As previously known, uremia is associated with an impaired immune response *via* several ways including cellular and humoral immune mechanisms. Patients on dialysis have lymphocytopenia, shortened life duration of lymphocytes and/or dysfunctional lymphocytes. Adequate $CD4^+$ lymphocyte count is essential to provide antibody production subsequent to vaccination[58,59].

Sengar *et al*[60] showed that an impaired immune response to HBV transmission is linked to a group of human leukocyte antigens (HLAs). Alper *et al*[61] determined an association between an inadequate response to HBV vaccine and HLA-DR3 and HLA-B8 in the Caucasian population. Some HLA groups were identified as predictors of low response to HBV vaccine. Pol *et al*[62] and Höhler *et al*[63] showed that low responders to HBV vaccine have enhanced expression of DRB 1 × 3, DRB 1 × 7 and DRB 1 × 14[62,63].

Walker *et al*[64] pointed out that nonresponders to HBV vaccine exhibit excess of HLA-DR7 and absence of HLA-DR1. In accordance with this study, patients with HLA-DR1, -DR5, -DR2, -DQ5 and-DP4 usually well respond to HBV vaccine and usually seroconvert[63].

Albumin level as a nutritional marker has been shown to directly affect antibody response to HBV vaccination. Brown *et al*[65] showed that patients with hypoalbuminemia are unable to produce adequate titers of antiHBs. Creatinine level is an indicator of protein intake and nutrition in the general population; however, due to lower excretion rate in patients with CKD, it is not a suitable marker for the assessment of nutritional status.

Age is another factor that may affect antibody response to vaccination[66]. Owing to the fact that bone marrow depression by aging, humoral and cellular responses are impaired in elderly patients. Patients at an advanced age have lymphocytopenia, monocytopenia and neutropenia as well as functional deterioration of these cells. Lymphocytes mediate humoral response against viral antigens in different steps. Only 15% of responders were older than 60 years; however, 55% of nonresponders were above 60 years of age[47]. Decline of antiHBs level is quicker in older patients, suggesting defective function of T lymphocytes and inadequate production of interleukins. In a study from Egypt, rate of seroconversion caused by HBV vaccination may be as high as 89% while it was only 51% in patients above 60 years of age[67]. Seroconversion rates significantly decline in older patients. The mean age of responders was 40.6 years while that of nonresponders was 59.6 years in the same study.

Also, male patients on dialysis have a significantly diminished antibody response to HBV vaccine when compared to female patients. Male gender is associated with an impaired response to vaccine. Seroconversion rates in female and male dialysis patients were 85.6% and 68.3%, respectively, and only 29% of patients with seroconversion were male[21].

Body weight, diabetes mellitus, hyperparathyroidism, erythropoietin resistance, vitamin D deficiency, use of low bio-incompatible dialysis material, iron overload, high number of blood product transfer, vitamin deficiency and hepatitis C positivity are well-known factors that are associated with poor response to vaccination[68-71]. On the other hand, Roozbeh *et al*[72] stated that age, gender, body mass index and serum albumin level do not significantly affect seroconversion rates.

Dialysis adequacy is probably a globally validated determinant of seroconversion rates. Seroconversion rates significantly correlate with renal function. Ghadiani *et al*[73] reported that seroconversion rates in patients with GFR < 15 mL/min, 15 to 60 mL/min and > 90 mL/min are 44%, 90% and 96%, respectively.

Controversy exists about the role of diabetes mellitus in response to HBV vaccine. Al Saran *et al*[52] concluded that the presence of diabetes mellitus has no significant effect on seroconversion rates. However, Chin *et al*[74] stated that dialysis patients with diabetes mellitus have a poor response to HBV vaccine.

Afsar *et al*[69] carried out a study in dialysis patients to evaluate the relation of erythropoietin resistance and response to HBV vaccine, and observed that erythropoietin resistance inversely influences the response to HBV vaccine.

A vast majority of reports determined that HCV positivity is related with a poor response to HBV vaccination[75]. However, some recent reports failed to demonstrate a negative impact of HCV positivity on response to HBV vaccination[76]. Table 2 summarizes the factors involved in the pathogenesis of unresponsiveness to HBV vaccination.

ROLE OF DIALYSIS THERAPY ON RESPONSE TO HBV VACCINATION

Patients on dialysis therapy have functionally and/or numerically defective regulatory T cells, leading to immunodeficiency and dysintegration between antigen presenting cells and CD4 T cells[77]. Accordingly, patients on HD had deteriorated neutrophil and macrophage

Table 2 Factors related to unresponsiveness to hepatitis B virus vaccination in the general population and patients with chronic kidney disease

General population	Patients with chronic kidney disease
Obesity	Dialysis
Smoking	Inflammation
	Administration route of vaccine
Diabetes mellitus	
	Hyperparathyroidism
Lymphomas	
	Co-existing HCV
Newborns and advanced age	Advanced age
Inflammation	Vitamin D deficiency
Celiac disease	Male gender
	Hypoalbuminemia
	Erythropoietin resistance
	IL-18 and *IFN-γ* gene polymorphisms

HCV: Hepatitis C virus; IFN: Interferon; IL-18: Interleukin-18.

functions resulting from inhibited chemotaxis and opsonization, both of which play a reactive role against host antigens. Selective T cell depletion is a frequently observed immunologic defect in dialysis patients, which causes diminished production of IL-1, IL-2, IL-6 and tumor necrosis factor-α[78]. In addition, interferon-gamma is produced by T cells and induces endocellular lysis of microorganisms and antigens.

Immunodeficiency is less frequently detected in patients receiving PD. They generally have depressed bactericidal activities of macrophages like opsonization, phagocytosis and lymphocytopenia, which reflects diminished peritoneal host defense[79]. Dialysis membranes and use of reaginic dialysis material are associated with excessive but non-effective immune response[80].

Regulation of immune response and interaction of mediators involved in immune response are complex processes and some unknown factors may influence their functions[81]. Roy *et al*[82] stated that decreased levels of cytokines that mediate the function of T helper cells may be associated with a low response to HBV vaccine. Deficiency of Th-1 like cells and defective or inadequate production of some cytokines by Th-1 cells are associated with immunosupression and a low response to viral agents[83]. IL-1, IL-2, IL-6, IL-12 and IFN-gamma are major cytokines involved in response to viral agents. Genetic polymorphisms and polymorphic variant of specific cytokines are associated with unresponsiveness to HBV vaccine[84].

FOLLOW-UP OF SEROCONVERSION OF HBV INFECTION

The recommended antibody titer to HBsAg should be > 100 IU/mL[85]. An important proportion of dialysis patients who achieve an adequate response (> 100 IU/mL) require a booster dose in every 5 years to maintain antiHBs titer[86]. Patients who failed to produce an adequate antibody response should undergo booster vaccination at 1 year and at 5 years of primary vaccination schedule[73].

The antibody titer < 10 IU/mL is defined as hyporesponse and > 10 IU/mL is accepted as positive seroconversion[87]. However, anti-HBs titer below 100 IU/mL is evidence of a low response.

Positive seroconversion (antiHBs > 10 IU/mL) does not always warrant protection against HBV infection in dialysis patients. Lombardi *et al*[88] suggested that antiHBs titer of at least 50 IU/mL should be a target level in HD patients.

Because the exact reason of lower serconversion rates to HBV vaccine is not known, the best strategy to overcome the unresponsiveness is to administer additional HBV vaccine. Wismans *et al*[89] showed that seroconversion rates after one and three additional 20 μg dose of HBV vaccine were 38% and 75%, respectively. Similarly, another study demonstrated a 61% seroconversion rate after additional vaccination[90].

DECREASE OF ANTIHBS TITERS

On the other hand, a group of dialysis patients who well respond to HBV vaccination and produce neutralizing antibodies against HBsAg do not maintain the antibody level with time. Although a decline in antiHBs titer by time is globally known in the general population as well as dialysis patients, it is significantly frequent and quicker in patients on RRT.

At the first year of vaccination, antiHBs > 10 IU/mL is induced in 82.5% of the general population by three doses of 20 μg, however, it was only 53% in dialysis patients by four doses of 40 μg[91]. At the third year of vaccination, the vast majority of HD patients have undetectable antiHbs level. American Association for the Study of Liver Diseases recommends annual screening of antiHBs titers and booster vaccination as antiHBs titer is around 10 IU/mL[40].

NEW INSIGHTS TO IMPROVE SEROCONVERSION RATES

Innovations in recombinant DNA vaccine technology may be hopeful to increase seroconversion rates and sustained response. IL-12-based vaccination therapies may restore HBV-specific CD4(+) T cell responses and augment seroconversion[92]. In agreement with Zeng *et al*[92], Lau *et al*[93] showed that combination of HBV vaccine with interferon-gamma or IL-12 may enhance therapeutic efficacy[93]. Accordingly, Somi *et al*[94] mentioned that IFN-adjuvanted HBV vaccination may be beneficial for hyporesponsive patients. In addition, nano-adjuvants seem to be frequently used to overcome unresponsiveness[95].

CONCLUSION

Despite increased awareness against HBV and impro-

vement in hygiene preservations, patients receiving RRT are still at an increased risk of HBV transmission. Additionally, due to immunosuppresive effect of uremia and dialyser membranes, chronicity of HBV infection is frequently observed. Rates of seroconversion induced by HBV vaccine is diminished in CKD patients when compared to the general population, which gradually decrease as renal functions deteriorate. Efficient dialysis is a major determinant of response to HBV vaccination. That is why early vaccination against HBV as soon as possible is essential to overcome unresponsiveness to HBV vaccine. In contrast to three doses of 20 μg HBV vaccine for the general population, patients on HD or PD usually require four doses of 40 μg HBV vaccine. Patients with CKD should be screened annually to detect decline of antiHBs titer and administered additional doses of HBV vaccine.

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