

# Evaluation of Response to Hepatitis B Vaccination in Chronic Hemodialysis Patients

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## ABSTRACT

**Background:** Hemodialysis (HD) patients are at an increased risk of acquiring hepatitis B virus (HBV) infection. Active HBV immunization in these patients is recommended. A response rate in HD patients is variable but generally lower than healthy individuals.

**Objective:** The aim of this study is to assess the response of HD patients to the HBV vaccine and correlate response and long-term immunity to various clinical and biomedical factors.

**Patients and Methods:** One hundred and one patients, with a mean age  $48.7 \pm 18.5$  years, received 40  $\mu\text{g}$  of HBV vaccine administered intramuscularly in the deltoid region at 0, 1, 2 and 6 months. The patients' responses to the vaccine were determined by measuring hepatitis B surface antibody (HBsAb) 6 weeks after the last injection and monitored thereafter at 3-month intervals.

**Results:** Seventy-one patients (70.3%) mounted a response with HBsAb  $>10$  mIU/ml 6 weeks following the fourth dose of vaccine, and thus were considered as adequate responders. Forty-nine (48.5%) patients mounted an excellent response with HBsAb  $>100$  mIU/ml 6 weeks after the fourth dose. Thirty patients (29.7%) were nonresponders. Responders were significantly younger than nonresponders ( $P = 0.01$ ). Gender, hemoglobin level, serum albumin, ferritin, parathyroid hormone level and hepatitis C virus infection had no effect on the response to the vaccine. Similarly, there was no difference in diabetic state and adequacy of HD between the two groups. Fifty-nine patients (88%) had persistent protective antibodies at 1 year, while eight (12%) lost such protection. Predictors of persistent immunity at 1 year were high HBsAb level at the completion of the vaccination regime and, to a lesser extent, young age.

**Conclusion:** A 70% response rate to HBV vaccine was observed in the cohort of this study. Young age predicts a favorable response to HBV vaccine in HD patients. High ( $>100$  mIU/ml) HBsAb levels achieved at vaccine completion predict persistent immunity at 1 year.

**Key words:** Hemodialysis, hepatitis B virus, seroconversion, vaccine

## INTRODUCTION

Approximately 2 billion people worldwide have been exposed to hepatitis B virus (HBV) infection and

350 million people have chronic HBV infection. It is estimated that 500,000–1.2 million people die every year because of diseases attributable to chronic HBV infection,

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such as liver failure and hepatocellular carcinoma.<sup>[1]</sup> Chronic hemodialysis (HD) patients are particularly prone to HBV infection. Increased risk in this population is related to excessive exposure to blood products, repeated vascular access entry and a state of immune deficiency. Hepatitis B (HB) infection in such patients may be associated with significant morbidity, such as acute and chronic hepatitis, liver cirrhosis and hepatocellular carcinoma, and may adversely affect the prospect of kidney transplant in these patients.<sup>[2]</sup> Furthermore, HD patients tend to become chronic carriers post-HBV infection more commonly than the general population.<sup>[3]</sup> Therefore, they potentially become a source of infection to fellow patients and medical staff.

Universal precautions, including dedicated rooms and equipment to treat HBV patients, are important steps in limiting the risk of spreading the infection among HD patients. Moreover, active HB vaccination in the HD population is crucial. Chronic HD patients who develop immunity after HB vaccination have a 70% lower risk of HBV infection and have a better survival and lower morbidity than no responders.<sup>[4,5]</sup> Despite utilizing the high-dose (40 µg) four-injection HB vaccine protocol, the response rate in HD patients remains significantly lower than the rate observed in the general population.<sup>[6,7]</sup>

In this study, the author presents a single-center experience with HB vaccination in chronic HD patients. Correlation between a response to the vaccine and several clinical and biological factors is analyzed and the relationship between the magnitude of response and persistent immunity at 1 year is examined.

## PATIENTS AND METHODS

A total of 101 patients, aged 16–81 years, who were negative for HB surface antigen and HB surface antibody (HBsAb) were included in this study that was conducted between January 1, 2008, and December 31, 2012. Patients receiving immunosuppressive drugs or with a history of cancer or chronic liver disease were excluded from the study. Thirty-nine patients were diabetic and 12 patients were positive for hepatitis C virus (HCV) antibody. The patients received 40 µg of recombinant HB vaccine (Engerix B, SmithKline Beecham Biologicals, Rixensart, Belgium) administered intramuscularly (IM) in the deltoid region at 0, 1, 2 and 6 months. The patients' responses to the vaccine were determined by measuring HBsAb 6 weeks following the last injection and monitored thereafter at 3-month

intervals. Achieving a serum HBsAB level  $\geq 10$  mUI/ml was considered as protective conversion. Responders with a development of HBsAb  $>10$  mUI/ml and  $<100$  mUI/ml at 6 weeks after the last injection were categorized as low immune responders, while those with levels  $>100$  mUI/ml were considered as high immune responders. The medical records were analyzed to correlate the response to the vaccine with several clinical and biological factors. These included age, sex, diabetic state, time from onset of dialysis to vaccine administration, HCV status, hemoglobin (Hb) level, serum ferritin, adequacy of HD as measured by percent reduction of urea (PRU) and Kt/V, intact parathyroid hormone (iPTH) level and C-reactive protein (CRP) level. Normalized protein catabolic rate (nPCR) as a measure of protein intake was calculated utilizing the following formula:

$$\text{nPCR in g/kg/day} = 0.22 + [(0.036 \times \text{blood urea nitrogen rise in mg/dl since last HD session} \times 24) / \text{hours since last HD}].^{[8]}$$

Statistical significance was calculated for differences between the means using unpaired *t*-test and Mann–Whitney test. The  $\chi^2$  test was performed for categorical data. Data are presented as a mean  $\pm$  standard deviation or as an absolute number and percentage when needed.  $P < 0.05$  was considered statistically significant.

The general consent was taken when patients underwent hemodialysis treatments and the associated interventions such as HB vaccination, erythropoietin treatments, etc. Because this study was descriptive in nature with no further intervention, this study was exempt from ethical approval.

## RESULTS

A total of 101 end-stage renal disease patients admitted to the chronic HD program between January 1, 2008, and December 31, 2012, received the hepatitis vaccine. The patients were aged 16–81 years, with a mean age of  $48.7 \pm 18.5$  years and a median of 48 years. Of the 101 patients, 65 (64.4%) were male, 39 (38.6%) were diabetic and 12 (11.9%) were positive for HCV antibody. Table 1 describes the clinical and biochemical characteristics of the patient population.

Seventy-one patients (70.3%) mounted an HBsAb level  $>10$  mIU/ml 6 weeks following the fourth dose of vaccine, and thus were considered to be adequate responders. Forty-nine (48.5%) patients mounted an excellent response

with HBsAb levels >100 mIU/ml 6 weeks postcompletion of the vaccine series. Twenty-two (21.8%) patients had a weak response with HB antibody levels >10 mIU/ml and <100 mIU/ml. Thirty patients (29.7%) were nonresponders.

Responders were significantly younger than nonresponders. Responders had a mean age of 45.7 ± 18.9 versus 55.8 ± 15.3 in nonresponders (*P* = 0.01) [Table 2]. Of the 52 patients aged <50 years, 42 (80.8%) mounted an adequate response compared with 29 of the 49 (59.2%) patients who were aged >50 years (*P* = 0.018) [Figure 1]. There was no difference between responders and nonresponders with respect to gender distribution, Hb level, serum albumin level, ferritin, PTH level and CRP levels. There was no significant difference in the prevalence of diabetes mellitus (DM) in responders and nonresponders. Adequacy of HD, as determined by PRU and Kt/V, was similar in the two groups. Duration on HD before vaccination had no effect on the response to the vaccine. Table 2 compares the clinical and biochemical parameters between responders and nonresponders. Table 3 compares the low and high responders.

Immune status at 1 year after completion of the HB vaccination was made available for 67 initial responders. Of these, 59 (88%) had persistent protective antibodies at 1 year, while 8 (12%) lost such protection. All but 1 of the 47 patients (97.9%) who mounted an excellent initial response had persistent immunity 1 year after completion of the vaccination series. However, 13 of 20 patients (65%) who had an initial weak response to the vaccine maintained immunity at 1 year. The odds ratio for losing protective immunity at 1 year following the completion of the vaccine in weak initial responders was 24.7 [95% confidence interval (CI): 2.8–220, *P* = 0.0040]. Predictors of persistent immunity at 1-year postvaccination are HbsAb level achieved at 6 weeks postimmunization (*P* 0.0005) and, to a lesser extent, younger age (*P* = 0.04).

## DISCUSSION

An HB vaccine seroconversion rate of 70.3% was achieved in 101 HD patients. Forty-nine patients (48.5%) mounted a high response with an HbsAb level >100 mIU/ml. A younger age predicted a positive response to the vaccine. No statistically significant difference was observed between responders and nonresponders with regards to gender, diabetic state, time on HD before vaccination, HCV infection, Hb, ferritin and PTH levels. The adequacy of dialysis, as measured by urea reduction

**Table 1: Demographic and clinical characteristics of all patients (n = 101)**

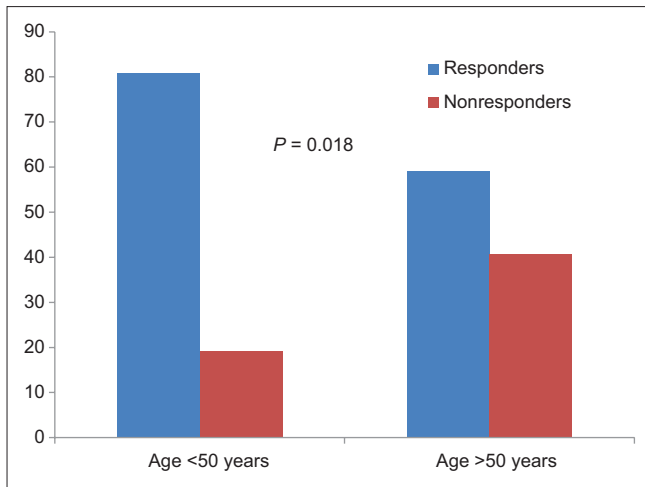
Parameter	Number (%) or mean ± SD
Male sex, n (%)	48 (67.6)
Age in years (mean ± SD)	48.7 ± 18.5
DM, n (%)	39 (38.6)
HCV Ab positive, n (%)	12 (11.9)
Time from onset of HD until vaccination in months (mean ± SD)	3.3 ± 2.6
Total protein (g/dl, mean ± SD)	6.8 ± 0.72
Serum albumin (g/dl, mean ± SD)	3.2 ± 0.44
Hb (g/dl, mean ± SD)	10.1 ± 1.6
Serum ferritin (µg/L, mean ± SD)	225.6 ± 208
iPTH (pmol/L mean ± SD)	56.66 ± 50.4
PRU (%) (mean ± SD)	62.78 ± 8.5
Kt/V (mean ± SD)	1.23 ± 0.20
CRP (mg/dl, mean ± SD)	1.439 ± 2.28
nPCR (g/kg/day, mean ± SD)	1.17 ± 0.33

DM – Diabetes mellitus; HD – Hemodialysis; HCV – Hepatitis C virus; Ab – Antibody; Hb – Hemoglobin; iPTH – Intact parathyroid hormone; PRU – Percent reduction of urea; CRP – C-reactive protein; nPCR – Normalized protein catabolic rate; SD – Standard deviation, NS – Not significant

**Table 2: Patients' demographic and clinical characteristics according to response to hepatitis B vaccine**

Parameter	Responders (n = 71)	Nonresponders (n = 30)	<i>P</i>
Male sex, n (%)	48 (67.6)	17 (56.7)	0.3 (NS)
Age in years (mean ± SD)	45.7 ± 18.9	55.8 ± 15.3	0.01
DM, n (%)	25 (35.2)	14 (46.7)	0.28 (NS)
HCV Ab, n (%)	10 (14.1)	2 (6.7)	0.29 (NS)
Time from onset of HD until vaccination in months (mean ± SD)	3.35 ± 2.75	3.26 ± 2.31	0.87 (NS)
Total protein (g/dl, mean ± SD)	6.72 ± 0.72	6.9 ± 0.69	0.3 (NS)
Serum albumin (g/dl, mean ± SD)	3.18 ± 0.46	3.1 ± 0.38	0.42 (NS)
Hb (g/dl, mean ± SD)	10 ± 1.68	10.27 ± 1.52	0.41 (NS)
Serum ferritin (µg/L mean ± SD)	202.4 ± 170.8	280.4 ± 269	0.16 (NS)
iPTH (pmol/L mean ± SD)	61.69 ± 51.1	44.13 ± 46.44	0.10 (NS)
PRU (%) (mean ± SD)	62.8 ± 8.6	62.8 ± 8.1	0.97 (NS)
Kt/V (mean ± SD)	1.23 ± 0.21	1.23 ± 0.19	0.95 (NS)
CRP (mg/dl mean ± SD)	1.19 ± 1.83	2.0 ± 3.0	0.19 (NS)
nPCR (g/kg/day mean ± SD)	1.17 ± 0.33	1.07 ± 0.26	0.11 (NS)

DM – Diabetes mellitus; HD – Hemodialysis; HCV – Hepatitis C virus; Ab – Antibody; Hb – Hemoglobin; iPTH – Intact parathyroid hormone; PRU – Percent reduction of urea; CRP – C-reactive protein; nPCR – Normalized protein catabolic rate; SD – Standard deviation, NS – Not significant



**Figure 1:** Response rate to hepatitis B vaccination among hemodialysis patients according to age

ratio and Kt/V, was similar in the two groups. There was no difference between the two groups in nutritional markers, as measured by serum albumin and nPCR. Persistent protective levels of HbsAb at 1 year were observed in 88% of the initial responders. Predictors of immunity maintenance at 1 year were high initial response and younger age.

The prevalence of HB infection among chronic HD patients had decreased significantly over the past decades.<sup>[9]</sup> Several factors have contributed to this decline such as implementation of policies regarding room segregation, equipment dedication and stopping the use of multidose medication vials. Routine use of erythropoiesis-stimulating agents in chronic HD patients has helped in reducing the exposure of such patients to blood products. Active HB immunization in these patients remains necessary, as sporadic outbreaks of HB infection in HD patients continue to occur.<sup>[10]</sup> HB vaccine introduced in the 1980s has definitely played a role in limiting HBV infection in HD patients. The Center for Disease Control recommends administering HB vaccine at a dose 40 µg by IM route in the deltoid region in HD patients at 0, 1 and 6 months. Most centers, however, incorporate the fourth dose given at month 2.<sup>[11]</sup> Despite the use of such high, more frequent dosing schedule, HD patients often develop a suboptimal response compared with the general population.<sup>[12]</sup>

The only readily available correlate of immune protection after HB vaccine administration is attaining an HBsAb level >10 mIU/ml 1–3 months after the last dose of the vaccine regimen. In fact, seroprotection may persist even if the level drops <10mIU/ml on subsequent testing. However, the recommendation is to administer a booster

**Table 3: Comparison between low responders (hepatitis B surface antibody >10, <100 mIU/ml 6 weeks postvaccine) and high responders (>100 mIU/ml)**

Parameter	Low responders (n = 22)	High responders (n = 49)	P
Male sex, n (%)	13 (59.1)	35 (71.4)	0.3 (NS)
Age in years (mean ± SD)	51.5 ± 16.9	43.1 ± 19.2	0.08 (NS)
DM, n (%)	7 (31.8)	18 (36.7)	0.7 (NS)
HCV Ab positive, n (%)	1 (4.5)	9 (18.4)	0.12 (NS)
Time from onset of HD untill vaccination in months (mean ± SD)	2.4 ± 1.9	3.8 ± 3	0.06 (NS)
Total protein (g/dl, mean ± SD)	6.9 ± 0.67	6.6 ± 0.73	0.2 (NS)
Serum albumin (g/dl, mean ± SD)	3.1 ± 0.46	3.2 ± 0.45	0.24 (NS)
Hb (g/dl, mean ± SD)	10.2 ± 1.34	9.9 ± 1.8	0.43 (NS)
Serum ferritin (µg/L, mean ± SD)	225.9 ± 165.8	191.8 ± 172	0.44 (NS)
iPTH (pmol/L, mean ± SD)	49.3 ± 29.1	67.7 ± 57.4	0.08 (NS)
PRU (%) (mean ± SD)	60.9 ± 8.6	63.6 ± 8.5	0.23 (NS)
Kt/V (mean ± SD)	1.19 ± 0.21	1.25 ± 0.2	0.23 (NS)
CRP (mg/dl, mean ± SD)	1.04 ± 0.88	1.26 ± 2.12	0.54 (NS)
nPCR (g/kg/day, mean ± SD)	1.21 ± 0.28	1.19 ± 0.35	0.38 (NS)

DM – Diabetes mellitus; HD – Hemodialysis; HCV – Hepatitis C virus; Ab – Antibody; Hb – Hemoglobin; iPTH – Intact parathyroid hormone; PRU – Percent reduction of urea; CRP – C-reactive protein; nPCR – Normalized protein catabolic rate; SD – Standard deviation, NS – Not significant

dose at that point. The protective efficacy of HB vaccine also involves the induction of memory B and T cells.

Various rates of seroprotection following HB vaccination in chronic HD patients have been reported. Such conflicting figures are owing to various factors such as sample size, age, weight and gender distribution; prevalence of DM; prevalence of HCV infection; duration on HD before the vaccine administration, adequacy of HD treatment and, possibly, genetic differences between populations. Variable dosing and scheduling regimens of the vaccine also contribute to the variable response rate in the HD population.

Peces *et al.* reported a seroconversion rate of 77.5% 1 month after vaccination in 80 seronegative HD patients who received a four-dose vaccination schedule (0, 1, 2 and 6 months), with 40 µg DNA-recombinant HB vaccine. A high antibody response was observed in 72.5% of patients, and nonresponse in 22.5% patients. Similar to the findings of the current study, a higher response rate



was observed in younger patients. There was no difference between responders and nonresponders with respect to sex, duration of HD, HD dose and nutritional status. Erythropoietin use and HCV infection had no influence on antibody responses to HB immunization.<sup>[13]</sup> The author observed similar findings in the cohort of the current study. Bel'eed *et al.* reported the outcome of HB vaccination in 247 renal patients, 149 of whom were chronic HD patients. They noted a seroconversion rate of 66% in HD patients. Responders tended to be younger and had a higher level of serum albumin.<sup>[14]</sup> An older report by Köhler *et al.* using three IM doses of 40 µg of HB vaccine in 99 HD patients resulted in a response rate of 50% in males and 66% in females. This is in contrast to a response rate of 95% in 29 healthy medical staff using a dose of 20 µg. The fourth dose given at 12 months improved the response rate from 56.5% to 71.7% in HD patients. The type of renal disease, length of time on dialysis and hematocrit did not influence the rate of immunization.<sup>[15]</sup>

In the cohort of the current study, a similar response rate was observed in HD patients with DM and those without DM. Most reported studies on this point support a notion that HD patients with DM respond less favorably to the vaccine. Chin, in a report of 97 HD patients vaccinated against HB, noted that 33 nonresponders, compared with 64 responders, had a higher prevalence of DM (70% vs. 39%). In addition, nonresponders were older, had lower serum albumin level and had higher dry weights than responders before HD was initiated.<sup>[16]</sup> Ocak and Eskiocak, in an HD patient cohort from Turkey, noted a lower but statistically insignificant seroconversion rate of 57.8% in 19 HD patients with DM compared with a rate of 70% in patients without DM. After the administration of additional booster doses during a 12-month period, the protective HBsAb levels in patients with DM improved but remained lower than levels in patients without DM.<sup>[17]</sup> A study conducted in Riyadh, Saudi Arabia, similarly, did not demonstrate a significant difference between responders and nonresponders with respect to DM.<sup>[18]</sup> Such conflicting influence of the diabetic state on the response to HB vaccine between populations may be related to genetic differences between populations.<sup>[19,20]</sup> Fabrizi *et al.* performed a systematic review of literature, looking at the impact of DM on the response to HB vaccine in dialysis patients. They identified 12 studies involving 1002 unique patients. Aggregation of study results showed a significant decrease in response rates among patients with DM versus patients without DM [pooled odds ratio = 0.52 (95% CI 0.38–0.71)].<sup>[21]</sup>

In the current study, the response to the vaccine in 12 patients with HCV infection was not significantly different from patients negative for HCV, a result which is comparable with that of other studies. Peces *et al.* reported that HCV infection did not influence the response to HB vaccination in their group of 80 HD patients.<sup>[13]</sup> However, some small studies observed a lower response rate in HCV-infected HD patients. Navarro *et al.* studied 36 chronic HD patients, 9 of whom were diagnosed as having HCV infection. The effective immunization rate was lower in HCV-infected patients (33.3% vs. 70.3%;  $P < 0.05$ ).<sup>[22]</sup> In another study by the same group, it was concluded that HCV infection influenced the level of immunity. Of the 43 HCV-negative cases, 27 (62.7%) obtained HBsAb levels  $>100$  IU/L, but only 3 of the 13 HCV-infected patients (23%) had an HBsAb  $>100$  IU/L ( $P < 0.01$ ,  $\chi^2$ ).<sup>[23]</sup> A systematic review conducted by Fabrizi *et al.* to determine the effect of HCV infection on the immunological response to HBV vaccine in dialysis populations identified eight studies with 520 unique patients on long-term dialysis and found no significant decrease in response rates among HCV-infected versus noninfected patients (pooled odds ratio = 0.621 [95% CI: 0.285–1.353]). These results were in concordance with the findings of the current study.<sup>[24]</sup>

A working strategy to improve the rate of successful immunization against HB in chronic HD patients would be to identify patients with chronic kidney disease (CKD) at an earlier stage, such as Stages 2 and 3, and offer vaccination to patients who are neither infected nor immune to the virus. Such a policy should be adopted in nephrology clinics providing care for CKD patients. This approach stems from the fact that a response rate to the HB vaccine is higher at the earlier stages of CKD.<sup>[25-27]</sup>

## CONCLUSION

Chronic HD patients have a lower response rate to the HB vaccine than healthy individuals, despite utilizing a more high frequent dosing protocol. Younger patients respond better to the vaccine. Obtaining high HBsAb levels ( $>100$  mIU/ml) at the completion of the vaccine ensures long-term immunity. Various demographic and biochemical factors including HCV infection and DM had no influence on the patients' response to the vaccine.

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## Conflicts of interest

There are no conflicts of interest.

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