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ORIGINAL ARTICLE

# Antibody Response Rates to Hepatitis B Vaccination in Children with Chronic Renal Failure: an Observational Study

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***Abstract:***

***Introduction:*** *Hepatitis B virus (HBV) infection is one of the most important factors increasing the mortality and the mobility in patients with chronic renal failure (CRF). There are a limited number of studies of pediatric patients with CRF regarding the response to double doses and protection rates. In this study, our aim was to compare the antibody levels and the respond rates to recombinant hepatitis B vaccine in children with chronic renal failure (CRF).* ***Materials and Methods:*** *In this prospective observational study, 36 children were included, who were in follow-up with a diagnosis of CRF, with a negative HBV serology and inadequate protective antibody levels. Prior to the vaccination program, HBV serologic tests and liver transaminase measurements were done in all patients. Patients under 11 years of age were administered 20 mcg, and patients older than 11 years were given 40 mcg of third generation recombinant DNA vaccine Euvax-B (LG Chemical Ltd.-Berk, Seoul-South Korea), into the deltoid muscle at months 0, 1 and 6. After vaccination, antiHBs levels were determined at the 1st, the 3rd, the 7th and the 12th months. A antiHBs level of ≥10 mlU/L was considered protective. Protection against hepatitis B infection as the ratio of ≥ 10 mIU / L. Analysis of variance, chi-square and T-test were used for the statistical analysis.* ***Results:*** *There were 21 female and 15 male patients. The mean age was 14.02 ± 4.2 years. Of all the patients, 11were at predialysis stage, 20 had continuous ambulatory peritoneal dialysis (CAPD), and 5 patients were treated with hemodialysis. In all groups of patients; protection rates of 58% in the 1st month, 92% in the 3rd month, 92% in the 7th month, 97% in the 12th month were achieved. The average vaccination antibody levels in all patients, according to the months were 210 mIU / L, 289 mIU / L, 336 mIU / L, and 336 mIU / L, respectively. There were no significant differences among the groups in terms of gender, protection rates and antibody titers (p> 0.05). The protection rate was found to be 67% in three patients receiving immunosuppressive therapy.The vaccination program was implemented in 18 patients who were on EPO treatment (Table 2). In these patients, the protective ratio was 83% and 94%, at 1 and 3 months, and 100% at 7 and 12 months. All patients with EPO treatment had an adequate antibody response.* ***Conclusion:*** *In our study, although the relative antibody response to hepatitis B vaccine was related to the immune regulation in pediatric patients with CRF, it did not seem to have a relationship with the type of dialysis. In addition, in the first year post-vaccination with a double dose, adequate antibody levels and level of protection is achieved in a substantial proportion of patients.*

**Keywords:** *Hepatitis B,Chronic Renal Failure, Dialysis, Vaccination*
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## Introduction

Hepatitis B virus (HBV) infection is one of the most important factors increasing the mortality and the mobility in patients with chronic renal failure (CRF), and in this group, the frequency of chronic hepatitis B carriers is significantly higher compared to the healthy population (1,2). In addition, chronic hepatitis is an important clinical problem that reduces the chances of renal transplantation in these patients, and after transplantation, due to hepatotoxic immune suppressive therapy, it can result in liver failure and death. Therefore, in patients with CRF, vaccination against hepatitis B and follow-up of vaccine-preventable diseases is of great importance (3,4). Due to the low seroconversion rate and the mean antibody titer, HBV vaccination is administered at varying doses and schemes in these patients (5,6). However, there are a limited number of studies of pediatric patients with CRF regarding the response to double doses and protection rates (2,4,7).

The risk of developing chronic liver disease after HBV infection is reported to be 3-10 % (1,3). The risk of HBV infection in dialysis patients was first introduced in 1960, and in a study published in 1974, the incidence of HBV was found to be 6%, whereas the incidence in the employees of the dialysis unit was 5% (6). In Turkey, according to the data of the Turkish Society of Nephrology, the rate of HBs Ag positive chronic hemodialysis patients varies between 5.4 and 28.5%, while it is 5-10% in healthy population (2,4). However, the frequency of carriers of HBV in hemodialysis patients in developing countries is still at high levels, varying between 10 and 22% (6,8).

In kidney diseases, there is an increased risk of HBV infection due to the immunodeficiency associated with the treatments for the primary disease, renal failure, as well as frequent hospitalization, intravenous procedures, blood transfusions, continuous ambulatory peritoneal dialysis (CAPD), and hemodialysis (HD) applications (5, 9, 10). In these patients, the main difficulty in eliminating the HBV infection is the low immunity rate after vaccination and the decrease in antibody levels more rapidly than normal (2, 11-14). Numerous inherited or acquired factors have been implicated in this lowered response, and the high frequency of recombinant human erythropoietin use among patients on maintenance dialysis has been suggested to play a pivotal role (13). However, in individuals with normal renal function, in five years, antibody titers drop to the protective value in only 15% of cases (8). More than 90% of healthy individuals develop immunity after vaccination, while the seroconversion rate of adult dialysis patients reached a rate of 50-75% with the application a double dose (2-4, 15). Therefore, it can be concluded that in pediatric dialysis and transplantation patients, the optimal response to hepatitis B vaccine is variable, depending on the immune system response (16).
In these patients, since the vaccination response consisted of sub-optimal antibody responses, higher doses of vaccine or an increasing number of vaccine doses were tested in order to obtain adequate protection, and the results were only partially successful (2,17,18). Due to the rapid decline in the protective antibody levels, different vaccination schemes are used to ensure the continuity of immunity (1, 19). The recommended method of administration is as follows: immunization at 0, 1, 2, and 6 or 12 months, and a booster vaccination when the antibody titer falls below the protective value (10 mU/mL) (2,6,18).

In light of studies in the literature, the aim of this study was to evaluate the antibody levels after vaccination and protection rates following the double dose and triple recombinant hepatitis B vaccine in pre-dialysis CRF, hemodialysis (HD), and continuous ambulatory peritoneal dialysis (CAPD) patients, with a negative HBV serology, in our pediatric nephrology clinic.

## Materials and Methods

### *Selection of the study group*

In this prospective observational study, 36 children were included, who were admitted to our pediatric nephrology clinic between June

2006-February 2008 with a diagnosis of chronic renal failure, no previous history of HBV infection, no adequate protective antibody level against hepatitis B, and normal liver function tests. Of these children, 11 were pre-dialysis, 20 were CAPD, and 5 were hemodialysis patients. Prior to the vaccination program, HBV serologic tests and liver transaminase measurements were done in all patients. Vaccination was performed in 36 patients with negative serological testing. The vaccination program was implemented in 18 patients who were on EPO treatment.

***Vaccination Program***

The third generation recombinant DNA vaccine Euvax B (LG Chemical Ltd-Berk medicine, Seoul-South Korea) was applied into the deltoid muscle at a dose of 20 mcg in patients under 11 years, and at a dose of 40 mcg in patients older than 11 years at the beginning, the first month, and the sixth month (20). Vaccine was provided by the Provincial Health Directorate of Ankara.

***1 - Monitoring of the vaccine response***

From patients who were included in the vaccine immunization program, venous blood samples were obtained before vaccination, and on the 1st, 3rd, 7th, and 12th months, and were centrifuged without delay to determine the anti-HBs levels (20).

***2 - Antibody titers***

The hepatitis B serology and the anti-HBs titration of the patients were determined using Eliza. In the quantitative determination of Anti-HBs, a Beckman Coulter Access Immunoassay device and an Access HBsAg 2 commercial test kit was used. The response to the vaccine was classified as "no response" (anti-HBs <10 mIU/L), "low response" (anti-HBs = 10-100 mIU/L), and "high response" (anti-HBs> 100 mIU/L), depending on the anti-HBs antibody titration. Protection ratio was calculated as the ratio of the number of patients with Anti-HBs levels ≥ 10 mIU/L to the whole group.

***3 – Other***

Serum albumin levels under 3.5 g/dl were considered to be low. The glomerular filtration rate of the pre-dialysis patients was calculated according to the Schwartz formula (16).

***Statistical Evaluation***

Statistical analysis was performed with SPSS software, version 11.5. All continuous variables were presented as mean ± SD. For the comparison of the groups, for the repeated measures, the analysis of variance, the chi-square test, and the t-test were used. A p value <0.05 was considered significant.

***Ethics***

The study was approved by the local ethical committee of the Pediatric Hematology Oncology Education and Research Hospital, and an informed consent was obtained from all patients.

**Result**

The distribution of patients according to their age, gender, and treatment is given in Table 1.

**Table 1: The distribution of patients according to their age, gender, and treatment**

| | n | Gender F/M | Mean Age ( ± 2sd) Year |
|---|---|---|---|
| **Pre-dialysis** | 11 | 5/6 | 8-19 (14.1±3.0) |
| **CAPD** | 20 | 7/13 | 2.5-21 (13.9±5.2) |
| **Hemodialysis** | 5 | 3/2 | 13-18(15.8±1.9) |
| **Total patient** | 36 | 15/21 | 2.5-21 (14.2±4.2) |

Of the 36 CRF patients who were included in the vaccination program to follow the antibody response, 21 were female (58%) and 15 were male (42%). The age range of the patients was 2.5-21 years (mean 14.02 ± 4.2years). The clinical and demographic characteristics are in Table 2.

Vaccine responses and protection rates of the study group are shown in Table 3. In the first month, the non-response rate was 42% and the protection rate was 58%. In the 12th month, these rates were 3% and 97%, respectively.

**Table 2: Clinical, and demographic characteristics, antibody responses of patients with CRF (* No protective antibody response was measured in a total of four patients (two pre-dialysis and two CAPD patients) who did not present for the control at 12 months).**

| No | Alb gr/dl | Gender | Ages (year) | Renal disease | İ.S.T | EPO | Types of Dialysis | CRF Stage | Rapel dose | Antibody responses (mIU/ml) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | 1st mh | 3rd mh | 7th mh | 12th mh |
| 1 | 4,9 | K | 14 | VÜR | ∅ | ∅ | pre-dialysis | 4 | ∅ | 576 | 576 | 576 | * |
| 2 | 3,9 | E | 13 | unknown | ∅ | ∅ | CAPD | 5 | ∅ | 125 | 182 | 496 | * |
| 3 | 4,2 | E | 17 | VÜR | ∅ | ∅ | pre-dialysis | 4 | ∅ | 3,1 | 92 | 3,3 | 494 |
| 4 | 1,4 | K | 18 | FMF-A | ∅ | ∅ | SAPD | 5 | ∅ | 12 | 166 | 180 | 114 |
| 5 | 4,5 | E | 16 | SLE nefritis | + | + | hemodialysis | 5 | ∅ | 2,3 | 1,6 | 296 | 156 |
| 6 | 4,2 | K | 12 | Ch. GN | ∅ | ∅ | pre-dialysis | 3 | ∅ | 2,1 | 16 | 296 | * |
| 7 | 3,1 | E | 9 | FGS | ∅ | ∅ | CAPD | 5 | ∅ | 496 | 437 | 63,7 | 74 |
| 8 | 4,2 | K | 11 | Joubert syd. | ∅ | + | pre-dialysis | 4 | ∅ | 16 | 42 | 78,6 | 114 |
| 9 | 5,3 | K | 18 | Sekkel syd. | ∅ | + | hemodialysis | 5 | ∅ | 496 | 496 | 496 | 496 |
| 10 | 4,1 | K | 9 | MLD | + | ∅ | CAPD | 5 | + | 0 | 29,3 | 76 | 9,1 |
| 11 | 4,5 | E | 15 | VÜR | ∅ | + | hemodialysis | 5 | ∅ | 7,9 | 496 | 496 | 496 |
| 12 | 3,7 | K | 16 | JNF | ∅ | + | CAPD | 5 | ∅ | 496 | 496 | 496 | 496 |
| 13 | 3,6 | K | 14 | JNF | ∅ | + | CAPD | 5 | ∅ | 46 | 423 | 496 | 496 |
| 14 | 4,6 | K | 17 | VÜR | ∅ | + | hemodialysis | 5 | ∅ | 496 | 496 | 496 | 496 |
| 15 | 4,5 | K | 16 | NB | ∅ | ∅ | CAPD | 5 | ∅ | 0,3 | 56 | 496 | 496 |
| 16 | 2,3 | E | 11 | FGS | + | ∅ | CAPD | 5 | ∅ | 4,1 | 0 | 1,6 | 153 |
| 17 | 4 | E | 16 | VÜR | ∅ | + | CAPD | 5 | ∅ | 496 | 496 | 496 | 538 |
| 18 | 3,7 | E | 11 | PUV | ∅ | ∅ | CAPD | 5 | + | 0,7 | 1,3 | 3,8 | 31,7 |
| 19 | 4,8 | E | 15 | VÜR | ∅ | ∅ | pre-dialysis | 3 | ∅ | 6,2 | 271, | 496 | 496 |
| 20 | 3,5 | K | 18 | UP-O | ∅ | + | CAPD | 5 | ∅ | 496 | 496 | 496 | 456 |
| 21 | 4,2 | K | 5 | FGS | ∅ | + | CAPD | 5 | ∅ | 0 | 102 | 182 | * |
| 22 | 4,2 | K | 20 | FMF-A | ∅ | + | CAPD | 5 | ∅ | 96 | 496 | 496 | 496 |
| 23 | 4 | E | 14 | NB | ∅ | + | pre-dialysis | ? | ∅ | 9,2 | 40,7 | 136 | 216 |
| 24 | 4 | K | 13 | NB | ∅ | + | CAPD | 5 | ∅ | 122 | 85 | 118 | 96 |
| 25 | 4,4 | K | 19 | LMB-S. | ∅ | ∅ | pre-dialysis | 3 | ∅ | 496 | 496 | 496 | 98,6 |
| 26 | 3,2 | E | 8 | VÜR | ∅ | + | pre-dialysis | 4 | ∅ | 496 | 496 | 496 | 496 |
| 27 | 4,8 | K | 15 | VÜR | ∅ | ∅ | pre-dialysis | 4 | ∅ | 2 | 12 | 296 | 142 |
| 28 | 3,5 | K | 21 | FMF-A | ∅ | + | CAPD | 5 | ∅ | 496 | 496 | 496 | 396 |
| 29 | 3,7 | K | 20 | JNF | ∅ | + | CAPD | 5 | ∅ | 496 | 496 | 496 | 538 |
| 30 | 3,9 | K | 15 | FGS | ∅ | ∅ | CAPD | 5 | ∅ | 496 | 496 | 496 | 496 |
| 31 | 3,7 | E | 14 | MPGN | ∅ | ∅ | pre-dialysis | 5 | ∅ | 376 | 354 | 496 | 496 |
| 32 | 3,4 | K | 20 | JNF | ∅ | + | CAPD | 5 | ∅ | 76 | 126 | 496 | 496 |
| 33 | 4,4 | K | 17 | VÜR | ∅ | ∅ | pre-dialysis | 3 | ∅ | 2,1 | 92 | 229 | 186 |
| 34 | 3,8 | E | 8 | Nefrocalsinosis | ∅ | ∅ | CAPD | 5 | ∅ | 418 | 496 | 295 | 436 |
| 35 | 4,4 | E | 13 | U.V-O | ∅ | + | hemodialysis | 5 | ∅ | 0,3 | 48 | 30,7 | 55 |
| 36 | 4,3 | E | 2,5 | VÜR | ∅ | + | CAPD | 5 | ∅ | 4,9 | 538 | 538 | 538 |

**Table 3. Antibody responses and protection rates in chronic renal failure (CRF) patients by month after three doses of hepatitis B vaccine**

| Months | Non-response rate | | Low response rate | | High response rate | | Vaccine responses | Protection rates |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| **1** | 15 | 42 | 4 | 11 | 17 | 47 | 21 | 58 |
| **3** | 3 | 8 | 10 | 28 | 23 | 64 | 33 | 92 |
| **7** | 3 | 8 | 4 | 11 | 29 | 81 | 33 | 92 |
| **12** | 1 | 3 | 4 | 13 | 27 | 84 | 31 | 97 |

**Table 4. The analysis of the antibody responses and protection rates of 11 patients with pre-dialysis by month after three doses of hepatitis B vaccine**

| Months | Non-response rate | | Low response rate | | High response rate | | Vaccine responses (%) | Protection rates (%) |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | | |
| **1** | 6 | 55 | 1 | 9 | 4 | 36 | 5 | 45 |
| **3** | 0 | 0 | 6 | 54 | 5 | 45 | 11 | 100 |
| **7** | 1 | 9 | 1 | 9 | 9 | 82 | 10 | 91 |
| **12** | 0 | 0 | 1 | 11 | 8 | 89 | 9 | 100 |

No protective antibody response was measured in a total of four patients (two pre-dialysis and two CAPD patients) who did not present for the control at 12 months. The analysis of the antibody responses of 11 patients with pre-dialysis revealed a non-response rate of 55% and a protection rate of 45% at 1 month, while these rates were 0 and 100%, respectively, at 12 months (Table 4). Of the 11 patients in the pre-dialysis group, the stage of chronic renal failure was not effective for antibody response in 10 patients (4 patients in stage 3, 5 patients in stage 4, 1 patient in stage 5).

In the CAPD group, antibody responses of 20 patients were as follows: non-response rate of 30% and a protection rate of 70% at 1 month, and 6% and 94% at 12 months, respectively (Table 5).

In the hemodialysis group, antibody responses of 5 patients were as follows: non-response rate of 40% and a protection rate of 60% at 1 month, and 100% and 100% at 12 months, respectively (Table 6).

There was no statistically significant difference among the pre-dialysis, hemodialysis and CAPD groups with regard to rates of protection depending on the mean antibody titers obtained after immunization at 1, 3, 7, and 12 months ($p > 0.05$) (Figure 1) (Table 7). In all patients and groups, there was no statistically significant difference in protection rates and antibody responses in terms of gender ($p > 0.05$). Three patients were given immunosuppressive therapy during the study. Of these patients, two were treated with high-dose steroids (2 mg/kg/day, for 1 month), and one patient was treated with cyclophosphamide (500 mg/m²/dose, once a month).

The protection rates of these patients at 1, 3, 7, and 12 months were 0%, 33%, 67%, and 67%,

**Table 5. Antibody responses and rates of protection by month after three doses of hepatitis B vaccine in the CAPD group**

| Non-response rate | | Months | | Low response rate | | High response Rate (%) | Vaccine responses (%) | Protection Rates (%) |
|---|---|---|---|---|---|---|---|---|
| n | % | % | n | % | n | | | |
| 6 | 1 | 30 | 4 | 20 | 10 | 50 | 14 | 70 |
| 2 | 3 | 10 | 3 | 15 | 15 | 75 | 18 | 90 |
| 2 | 7 | 10 | 2 | 10 | 16 | 80 | 18 | 90 |
| 1 | 12 | 6 | 3 | 16 | 14 | 78 | 17 | 94 |

respectively. The hemodialysis patient who was treated with cyclophosphamide did not have an antibody response at the first and third months, however the patient had a high response at 7 and 12 months. Patient number 10, who was treated by CAPD and was taking steroids, had a non-response at the first month and a low response at 3 and 7 months. However, the patient became unresponsive again at the 12th month. This patient was administered a fourth dose of the

**Table 6. Antibody responses and rates of protection by month after three doses of hepatitis B vaccine in the hemodialysis group**

| Months | Non-response rate | | Low response rate | | High response rate | | Vaccine responses | Protection Rates (%) |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | | |
| **1** | 2 | 40 | 1 | 20 | 2 | 40 | 3 | 60 |
| **3** | 1 | 20 | 1 | 20 | 3 | 60 | 4 | 80 |
| **7** | 0 | 0 | 1 | 20 | 4 | 80 | 5 | 100 |
| **12** | 0 | 0 | 1 | 20 | 4 | 80 | 5 | 100 |

Patient number 16, who was treated by CAPD and was taking steroids, had a non-response at the first, third, and seventh month, whereas a high response was observed at 12 months. The protection rates of 33 patients, who did not receive immunosuppressive therapy, were 76%, 97%, 94%, and 93% at 1, 3, 7, and 12 months, respectively. A statistical evaluation was not possible since there were a small number of patients receiving immunosuppressive therapy.

The vaccination program was implemented in 18 patients who were on EPO treatment (Table 2). In these patients, the protective ratio was 83% and 94%, at 1 and 3 months, and 100% at 7 and 12 months. All patients with EPO treatment had an adequate antibody response. Of the three patients who had EPO treatment and did not have an adequate antibody response at the first month (patient numbers: 5, 21, 35), two were in vaccine (booster dose). the hemodialysis group (patient numbers: 5 and 35), and one (patient number: 21) was a CAPD patient. The only patient with EPO treatment, who did not have adequate antibody response at 3 months (patient no: 5), was a hemodialysis patient. The protection rates of 18 patients who did not receive EPO were 44%, 89%, 83%, and 93%, at the 1st, 3rd, 7th, and 12th months, respectively. In the 12th month, the protection rates of the patients who did and did not use EPO were similar (p = 0508). However, in the 12th month, the mean antibody levels were 403 mIU/L in the users of the EPO, and 261 mIU/L in the non-users, with a significant difference (p = 0.025).

## Discussion

Hepatitis-B is stili a problem in dialysis units and the number of nonresponders to hepatitis-B vaccination is relatively high in patients on regular hemodialysis treatment. The reason for low seroconversion rates in chronic renal failure

**Table 7. The mean antibody titers and protection rates in the pre-dialysis, hemodialysis, and CAPD groups, after three doses of the hepatitis B vaccine**

| Group | Months | Antibody responses | | Mean antibody Titers (mIÜ/L) |
|---|---|---|---|---|
| | | n | protection rates (%) | |
| **Total n: 36 (12. months n: 32)** | 1 | 21 | 58 | 210 |
| | 3 | 33 | 92 | 289 |
| | 7 | 33 | 92 | 336 |
| | 12 | 31 | 97 | 336 |
| **Pre-dialysis n: 11 (12. months n: 9)** | 1 | 5 | 45 | 156 |
| | 3 | 11 | 100 | 210 |
| | 7 | 10 | 91 | 302 |
| | 12 | 9 | 100 | 304 |
| **CAPD n: 20 (12.ayda n: 18)** | 1 | 14 | 70 | 236 |
| | 3 | 18 | 90 | 323 |
| | 7 | 18 | 90 | 346 |
| | 12 | 17 | 94 | 351 |
| **Hemodialysis (12.months n: 5)** | 1 | 3 | 60 | 213 |
| | 3 | 4 | 80 | 307 |
| | 7 | 5 | 100 | 362 |
| | 12 | 5 | 100 | 339 |

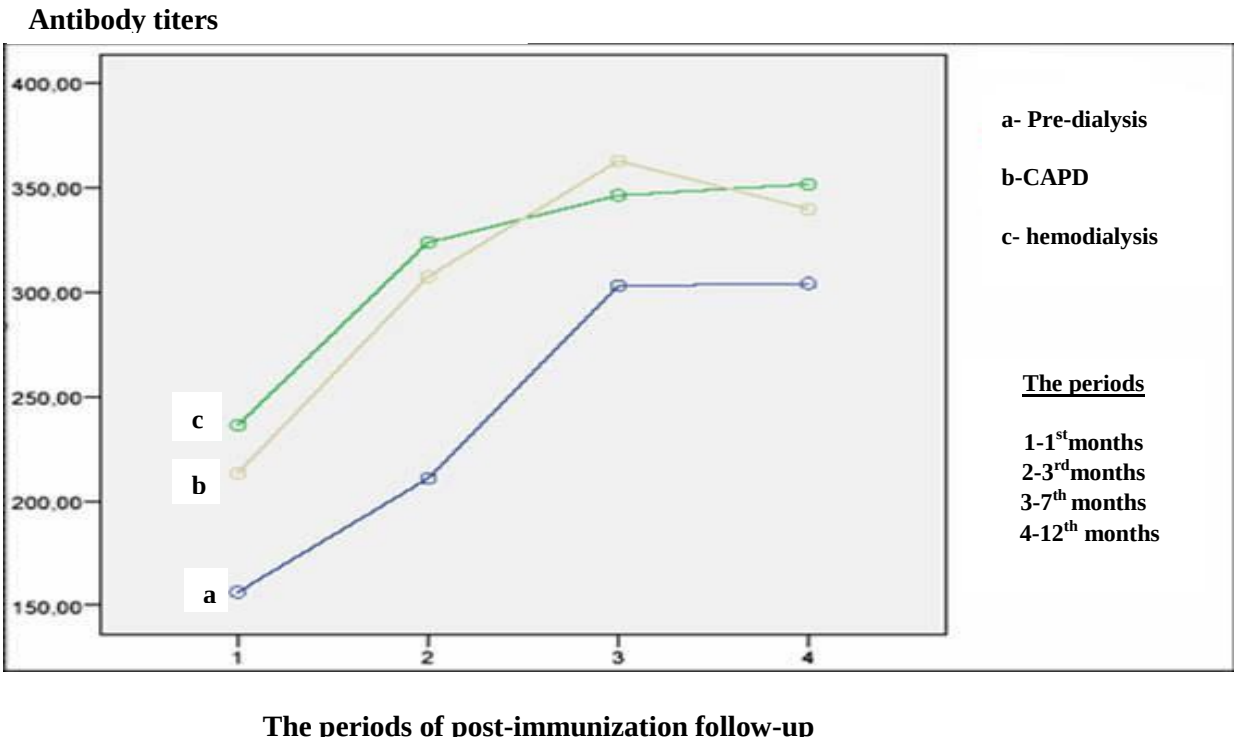


**Figure 1. Anti-HBs titers at 1, 3, 7, and 12 months in pre-dialysis, CAPD and hemodialysis patients. There was no statistically significant difference among the pre-dialysis, hemodialysis and CAPD groups with regard to rates of protection depending on the mean antibody titers obtained after immunization (p> 0.05).**

(CRF) patients is poorly understood (14, 20). In our study, we determined a protection rate of 97% per month, and mean antibody levels of 337 mIU/L, respectively, at 12 months, after a double dose of recombinant hepatitis B vaccine (administered at 0, 1, and 6 months). No differences were found in the protection rates and antibody levels with regard to the type of dialysis. In three patients receiving immunosuppressive therapy, the protection rate was 67%, while the protection rate in 18 patients who did not use EPO was 93%. Although the relative antibody response to vaccination in this study was associated with immune regulation, it did not seem to be related to the type of dialysis, which is a remarkable finding. A double dose and three-dose vaccination regimen seems to be beneficial in reducing the rate of HBsAg carrier and to provide sufficient protective antibody levels in children with chronic renal failure who are candidates for transplantation without adequate protective antibody levels.

In Turkey, studies in HD patients have reported the HBsAg and anti-HBs positivity varying between 3.1-27.9% and 32.5-68.4%, respectively, (7). There are various opinions about the vaccine dose and the vaccination schedule in patients with CRF (1). The most commonly used protocol is the application of recombinant hepatitis B vaccine at 0, 1 and 6 months. A double dose of the vaccine provides an increase of 20-40% in the response rate. There is an established relationship between the increasing dose of the vaccine and the antibody response (3). After three doses of vaccination, the overall anti-HBs response was 75-100%, which is higher compared to the single dose (17,18). In children with progressive CRF, protection with hepatitis B vaccine in the early stages may reduce the need for a higher dose later (1).

In our study, in children with advanced stage CRF (mean age: 14.2 years), by double dose vaccination at 0, 1 and 6 months, a protection rate of 97% was achieved. In a study with 15 HD patients aged between 12-60 years, Gündüz et al. (21) applied 40 mcg of recombinant hepatitis B vaccine at 0, 1, 2 and 6 months, and the rate of protective antibodies were reported as 20%, 67%, 64%, and 64% at 1, 2, 6, and 12 months, respectively. There was no association between the vaccine response and parameters such as T-lymphocyte count, function, and major histocompatibility antigens. In our study, however, of the 36 patients, three were administered the vaccine concomitantly with immunosuppressive therapy. The protection rate was 0%, 33%, 67%, and 67%, at 1, 3, 7, and 12 months, respectively. The immunosuppressive therapies disrupt the cellular and humoral immune response (22). Therefore, antibody response is low (50-60%) in users of immunosuppressive therapy and the developed antibody titer is usually ephemeral (7). Despite the small number of patients, the obtained result shows that immunosuppressive therapy may result in low or insufficient antibody response. The assessment of the response to the vaccine seems to be important in terms of follow-up of the immune response in patients with chronic renal failure (23). In our study, the anti-HBs positivity (97%) seems to be higher in hemodialysis patients compared to the literature. This is probably due to regular and complete vaccination of patients according to the defined vaccination program.

Gender appears to be an important factor in the response to HBV vaccine (21). The available literature suggests that seroconversion in women is higher (1, 3). However, we did not find any difference between the genders with respect to the response to the vaccine.

In a total of 21 pediatric patients with CRF (13 HD, 8 CAPD), Drachman et al. (24) administered 20 mcg of plasma-derived vaccine at 0, 1, and 6 months, and obtained 34% protection. In the unresponsive patients, they administered a monthly dose of 40 mcg until the anti-HBs became positive. They achieved a protection of 33%, 76%, and 86% at the third, fourth, and fifth injections, respectively. In a series of 56 adult patients, Kosar et al. (25) applied 20 mcg of recombinant hepatitis B vaccine in 36 patients, and 40 mcg in 20 patients

at 0, 1, and 6 months, and determined the antibody responses. In patients receiving a single dose of the vaccine, the protection rate was 69%, whereas that of the double dose group was 85%. The difference between the two groups was statistically significant ($p < 0.05$).

Bak et al. (26) applied the recombinant hepatitis B vaccine at a dose of 20 mcg at 0, 1, and 2 months in eight CRF patients treated with HD between 5 to 16 years of age, and obtained an adequate immune response in 5 (63%) cases. After application of three doses of 5 mcg of plasma-based vaccine to 18 HD and 10 pre-dialysis patients, Atabek et al. (27) achieved a vaccine response of 70% in the pre-dialysis group and 61% in the hemodialysis group, with an overall response of 68%. The difference between the two groups was not statistically significant. In our study, a protection of 92% and 97% was obtained in the 7th and the 12th months, with antibody titers above 100 mIU/L in 80.5% and 84.3% of the patients, respectively. In our study group, the geometric mean antibody titer at 12 months was 336 mIU/L. A booster dose was required in two patients. However, Taal et al. (28) applied 30 mcg of hepatitis B vaccine into the deltoid muscle in 36 HD patients at 0, 1, 2, and 4 months, and achieved protective antibody levels in 69% with a mean antibody level of 372 mIU/L. The rate of protection is lower than that of our study, while the mean antibody level is higher. This and similar studies show that immunization dose is effective in the antibody response, and double dose vaccination results in a better antibody response.

In our study, patients in the pre-dialysis and HD groups responded to vaccination with a protection rate of 100% at 12 months, while one patient (6%) in the CAPD group did not respond to vaccination, and vaccine protection rate in this group was 94%. There was no statistically significant difference between the groups. Doğukan et al. (29) administered 40 mcg of recombinant hepatitis B vaccine to 55 adult patients with CRF (15 pre-dialysis, 11 CAPD, and 29 HD) at 0, 1, 2, and 6 months, and achieved an overall protection rate of 78%. Although they found a higher vaccine response in pre-dialysis and CAPD patients, the difference was not statistically significant. However, Mitwalli et al. (30) achieved a higher response in CAPD patients compared to HD patients. In this study, there was no statistically significant difference among the pre-dialysis, hemodialysis and CAPD groups with regard to rates of protection depending on the mean antibody titers obtained after immunization at 1, 3, 7, and 12 months ($p > 0.05$) (Figure 1) (Table 7). The increase in the vaccine response rates may be associated with the early diagnosis due to more stringent screening of dialysis patients in terms of HBV infection, separation of dialysis machines, and the reduced frequency of blood transfusions.

Yao-Lung Liu et al. (31) followed adult patients with vaccination for a period of two years, and at the end of two years, the level of protective antibodies in the hemodialysis and pre-dialysis groups were found to be 60% and 50%, respectively, with no significant difference ($p = 0.41$). At the same time, they reported that the protection rate was inversely proportional to age, yet independent of gender, duration of dialysis, diabetes, HCV infection, hemoglobin, albumin, or ferritin levels. In their study of patients treated with HD, Navarro et al. (32) found that age, duration of HD, and albumin levels do not affect the response to the vaccine, whereas the response was higher in women, and HCV positivity reduced the vaccine response. Similar studies also claimed to obtain a better antibody response at young age (29, 30, 33). In our study, no relationship was identified between antibody response and the type of dialysis replacement therapy. In our study, which was conducted in the pediatric age group, high protection was obtained in the first year.

Response to the vaccine was shown to be correlated with serum PTH and EPO levels, and the degree of uremia (13, 34). Recent data indicate that EPO have humoral and cellular immunomodulating properties. As an example, EPO increases immunoglobulin production and proliferation of human B cells and B-cell lines

(34,35). In a study of Anandh et al. (35) comparing the response to subcutaneous vaccination once or twice a week for six weeks, the antibody response was shown to be better in those treated with EPO. Furthermore, in this study, age, gender, and primary renal disease were found to have no role in the antibody response. However, there are studies showing that the use of EPO is negligible in antibody response (36). In our study of 18 patients with chronic renal failure treated with EPO, all responded to vaccination with a protection rate of 100% at 12 months. In patients who were not treated with EPO, the protection rate was 93%. Despite a similar protection rate, the mean antibody levels of the EPO-users at 12 months was 403 mIU/L, and that of the non-EPO users was 261mIU/L, and the difference was statistically significant ($p = 0.025$).

## Conclusion

In this study, it was determined that in patients with chronic renal failure, with a double dose vaccination with recombinant hepatitis B vaccine at 0, 1 and 6 months, an adequate antibody response was achieved in 97% of patients in the first year. The relative antibody response to vaccination seems to be associated with immune regulation and independent of the type of dialysis. In addition, for an effective prophylaxis, anti-HBs titers should be followed closely, re-vaccination should be done in patients with low antibody response, and additional methods of protection should be considered.

### *Limitations of the study*

The limiting factors of our study are the small number of patients, lack of follow-up of the previous vaccination scheme, and anti-HBs titers and lack of the antibody titers of patients with low antibody response in the later period. However, our results are consistent with the literature, with a protection rate of 97% at 12 months in all dialysis groups. More extensive studies on the application site, the dose and the schedule may provide more useful information on the efficacy of the hepatitis B vaccine.

### *Disclosure*

The authors report no conflicts of interest in this work.

### *Abrevations*

*VÜR: vesicoureteral reflux*
*FMF-A: Familial Mediterranean fever, amyloidosis*
*SLE: Systemic lupus erythematosus*
*Ch. GN: chronic glomerulonephritis*
*FGS: Focal segmental glomerulosclerosis*
*JNF: Juvenil Nefronofitisis*
*PUV: Posterior Urethral Valve*
*UP-O: Ureteropelvic obstruction*
*LMB- S: Laurence Moon Biddle Syndrome*
*UV-O: ureterovesical obstruction*
*EPO: Eritropoetin*
*MPGN: Membranoproliferative glomerulonephritis*
*İST: immunosuppressive therapy*
*CRF: Chronic renal failure*
*CAPD: continuous ambulatory peritoneal dialysis*
*Alb: albumine*
*MLD: Metachromatic Leukodystrophy*
*NB: Neurogenic bladder*
*Mh:months*

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