ORIGINAL ARTICLE

Response rates to HB vaccine in CKD stages 3-4 and hemodialysis patients

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Background: Hepatitis-B virus (HBV) infection is a big problem in chronic kidney disease (CKD) population. We attempted to compare the response rate to HB vaccine in CKD stages3-4 patients with that in hemodialysis (CKD stage-5; HD patients) and medical staff. **Materials and Methods:** Three hundred and three participants were enrolled into the study to test the seroconversion rate after vaccination. Participants formed three groups: Group-A:HD patients, Group-B: diagnosed with CKD stages 3-4, and Group-C: healthy medical staff. CKD stages 3-4 participants were vaccinated from February to November 2010. HD patients were vaccinated at the time of initial HD. While the medical staffs were vaccinated at the time they started working at the hospital. Group-A, Group-B and Group-C received four 40µg (in 0,1,2 and 6 months), three 40µg (0, 1 and 6 months) and three 20µg (0, 1and 6 months) doses of HB vaccine, respectively. Three months after completion of the vaccination schedule, seroconversion and seroprotection rates in each group were investigated. **Results:** Seroconversion rates were 44.3%, 89.7%, and 96.2% for groups A, B and C, respectively. CKD stages 3-4 patients showed higher response rate than dialysis patients [$\chi^2(1):30.6$, $P<0.001$]. But a significant difference in the seroconversion rate between CKD stages 3-4 patients and medical staffs was not observed [$\chi^2(1):3.4$, $P=0.064$]. Multivariate analyses showed patients with more advanced CKD and who were older had less seroconversion rates [odds ratio: 0.09(95%CI: 0.04 - 0.25) and [odds ratio: 0.39(95% CI: 0.18-0.85)], respectively. But sex was not associated with seroconversion ($P>0.05$). **Conclusion:** Stages 3-4 patients with higher dosages of routine HB vaccine had higher seroconversion rate than HD patients. Future studies should evaluate the recommended dosage of HB vaccine among these patients.

Key words: Chronic kidney disease, hemodialysis, Hepatitis-B vaccine, seroconversion

INTRODUCTION

One of the most serious infectious diseases in the world is Hepatitis-B virus (HBV). It is estimated that 200–500 million people are infected by the virus in the world;[1] 360 million have chronic infection and 600,000 die by acute hepatitis, liver fibrosis, or hepatocellular carcinoma each year.[2] Hepatitis-B infection is difficult to treat, that is why prevention by Hepatitis-B vaccine (HB vaccine) is the most efficient way to tackle the problem. HB vaccine has been available since 1982.[3] Today's HB vaccine contains 20 µg HB surface antigen (HBsAg) along with 0.5 mg aluminum salt as adjuvant. In the general population, seroprotection is defined by an HB surface antibody (HBsAb) titer greater than10 mIU/ml. The HB vaccine has been confirmed to be safe, and there is no evidence indicating it causes any complications or side effects. Seroprotection rates have been attained in up to 95% of healthy individuals with a 23 standard dose of vaccination.[2] In another study on Iranian population standard HBV vaccination has resulted in an immune response in 57.9% of subjects.[4] There are some studies about the prevalence of chronic HBV infection in general population of Iran.[5,6] These studies have shown that because of the vaccination of newborns against HBV, since 1992, prevalence of chronic HBV infection has reduced.

Due to exposure to blood products, hemodialysis (HD) patients have a higher risk for several infections.[7] These patients are at increased risk for becoming carriers of the HBV, which would lead to eventual cirrhosis and liver carcinoma.[8]

Because of erythropoietin, the incidence of HB infection has reduced.[9] However, occurrence of HB infection in HD units continues to occur with different frequencies.[7,10-14] HB vaccine has reduced the number of HB infections in patients with chronic kidney disease (CKD).[15]

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In HD patients, the effectiveness of HB vaccine to seroconversion is lower than in the general population.[16-19] Patients with end-stage renal disease (ESRD) have several defects in both the humoral and cellular immune response,[20,21] which results in reduced production of antibody.[7,15,22]

One study has suggested that to improve this response rate, patients should be vaccinated at the early stages of CKD and before requiring dialysis or transplantation.[23]

In one Iranian population study, the response rate to vaccination in predialysis patients was the same as in dialysis patients.[24]

One of the largest studies performed on this issue enrolled 61 renal failure patients. The authors concluded that patients who were not on dialysis had a better immune response to HB vaccine than the patients who were on dialysis.[25] However, the best strategy for vaccination at CKD stages 3-4 patients before HD has not been ascertained yet.

Our current prospective study aimed to compare seroconversion rates between three groups of patients namely, CKD stages 3-4, under HD and medical staff as the control group. We also hoped to be able to identify some of the possible parameters that could influence the response rates to HB vaccine.

MATERIALS AND METHODS

In this clinical trial 303 participants have been involved. According to the glomerular filtration rate(GFR), the patients were divided into three groups: HD patients (Group-A, GFR<15 ml/min), patients with CKD stages 3-4 (Group-B, 15< GFR< 60 ml/min), and medical staff (Group-C, GFR> 90 ml/min). All CKD and HD patients were receiving care at a kidneydialysis center in the Iranian provincial capital of Zanjan.

All CKD participants were vaccinated from February to November 2010. . HD patients were vaccinated at the time of initial HD and medical staff at the time of being hired.

The vaccination protocol for groups A and C was as follows: Group-A received 40 μg at 0, 1, 2 and 6 months and Group-C received 20 μg at 0, 1 and 6 months. In addition, the vaccines were injected into the deltoid muscle and according to the policy of the hospitals and HD wards the levels of antibody production of both groups were checked 3 months after the last dose of injection.

We used both the CockcroftGault (C–G) and modified diet in renal disease (MDRD) formulas to determine kidney function, GFR.

For Group-B, the entry criteria included a GFR of less than 60 ml/min and more than 15 ml/min, as was determined by using the C-G formula [(140 – age) × lean body weight/ serum creatinine × 72] and estimated glomerular filtration rate (eGFR), which was calculated by using the abbreviated modified diet in renal disease (MDRD) formula, where eGFR (ml/min)/1.73m^2 =186 × (Creatinine/88.4)$^{-1.154}$ × (age)$^{-0.203}$ × 0.742 (if female) or 1.21 (if African American).[15] Patients in Group-B were withdrawn from the study if their renal function had deteriorated to the point that dialysis treatment was needed.

The exclusion criteria for Group-B included: hypersensitivity to HB vaccine, a history of previous HB infection and taking immune suppressive medications as well as patients with known lymphoproliferative disorder.

All participants in Group-B signed a consent form after being informed about the study. Before enrollment, patients were tested for HBsAg, anti-HBc and anti-HBs antibodies by enzyme-linked immunosorbent assay (ELISA) methods. All patients of Group-B who were identified as HB infection negative and anti-HBs negative started a vaccination schedule consisting of recombinant vaccine 40 μg at 1, 2 and 6 months. Vaccine was administered intramuscularly into the deltoid muscle. The vaccine was well tolerated; no patient had a serious adverse event attributable to the vaccine, and no patient withdrew from the study because of an adverse event. All patients received their vaccinations at the clinic.

HBsAb was measured by using ELISA methods at virology laboratory of Vali-e-Asr Hospital. Anti-HBs titers are expressed in mIU/ml. For all the participants, Anti-HBs antibodies were measured 3 months after the completion of the vaccine schedule. Anti-HBs titers less than 10 mIU/ml were defined as non-seroconversion. Antibody titers more than 10 mIU/ml were considered as seroconversion, and HBs titers above 100 mIU/ml were considered seroprotective level, for groups A and B. Antibody titers more than 10 mIU/ml were considered as seroprotection for Group-C. For all groups, patients with antibody levels <10 mIU/ml were considered non-responders.

All the HD patients were on bicarbonate HD for 3.5 4 h, three times a week, by using 1.72.1 m^2 capillary high flux polysulfone dialyzer and a dialysate flow rate of 300 and 350 ml/min. Hematocrit levels were maintained between 30 and 38% by administration of appropriate doses of recombinant erythropoietin.

The study was approved by the research ethics committee of the Zanjan University of Medical Science (Ethics No: 19/3-3/236). Trial Registration Number: IRCT 138905163325N4

Statistical analysis

Baseline characteristics are presented as mean ± SD or median with 25th and 75th percentiles, depending on the underlying distribution. Continuous variables were compared in three groups using analysis of variance or KruskalWallis test, when appropriate, while discrete variables were compared by using chi-square test. We used *t*-test or Mann–Whitney U-test (for non-parametric samples) and chi-square test to compare baseline characteristics between seroconverters and non-seroconverters. A *P*-value of less than 0.05 for two-sided univariate test was considered statistically significant.

A logistic regression model was used to identify important predictors of seroconversion. Variables included in multivariate analysis were patients' age, sex and GFR. All models were tested for interaction.

RESULTS

Three hundred three HBsAg negative participants [101 males (33.3%) and 202 females (66.6%), with a mean age of 44.30 years]were enrolled for this study. Table-1 presents the characteristics of the study population.

Table 1: Characteristics of study population at enrollment

Variables	No. (%)
Age (years)	44.3 ± 17.9 (30-59)*
Age > 60 years	73 (24.1)
Male gender	101 (33.3)
Weight (kg)	68.7 ± 10.9 (60-78)
Creatinine (mg/dl)	2.3 ± 1.9 (0.8-3.8)
GFR (CockcroftGault) (ml/min/1.73 m^2)	69.4 ± 48.8 (14.6-108.3)
GFR (MDRD) (ml/min/1.73 m^2)	57.0 ± 39.7 (15.2-90.1)
Anti-HBs levels (mIU/ml)	224.4 ±259.1 (20-324)
Seroconversion rate	242 (79.9)
Seroprotection rate	206 (68)

*Values expressed as Means SD (25th75th percentiles) and numbers (percentage)

Table 2 lists and compares demographic and laboratory data of the three study groups. Group-A comprised 49 males (55.7%) and 39(44.3%) females with a mean age of 58.8 years. Group-B consisted of 29 males (50%) and 29 females (50%), with a mean age of 57.7 years. Group-C included 23 males (14.6%) and 134 females (85.4%), with a mean age of 31.2 years.

Mean serum creatinine level of CKD patients (Group-B) was 2.12 ± 0.61 mg/dl; according to C-G formula, the creatinine clearance amounted to a GFR mean of 35.4 ± 12 ml/min with an eGFR of 32.2 ± 9.9 ml/min/1.73 m^2 as calculated by MDRD formula. Based on the above data, the participants of Group-B had stage 3 and/or stage 4 of CKD.

For HD patients (Group-A) the GFR mean according C-G formula was 13.4 ± 1.3 ml/min, while the GFR mean according MDRD formula was 11.9 ± 3.3 ml/min/1.73 m^2.

GFR according both MDRD and C-G was lower in HD patients [*P* <0.001, 95% confidence interval (CI: 19-24]. There were no significant gender and age differences between groups A and B.

Compared to groups A and B, participants in Group-C were younger [*P* <0.001, t (243): 20.5 and t(213):17.2], and there were more females [χ^2(1):45.73 and 28.8, *P* <0.001] than males.

Two hundred and forty-two individuals out of the 303 participants in the study (79.9%) seroconverted after the vaccine schedule (anti-HBs levels ≥ 10 mIU/ml) as measured 3 months after the last vaccine was administered. The mean peak of anti-HBs titer was 224.4 ±259.1 IU/l (20324 IU/l) [Table 1].

Seroconversion rate in HD patients was 44.3%, for Group-B patients 89.7% [χ^2(1):30.6, *P* <0.001] and for Group-C 96.2% [χ^2(1):87.1, *P* <0.001]. A significant difference in seroconversion rate between Group-B patients and medical staff was not observed (χ^2(1):3.4, *P*<0.064) [Table 2].

Table 2: Comparison of different variables between study groups

Variables	Group-A (HD patients) (n = 88) (%)	Group-B (CKD patients) (n = 58) (%)	Group-C (Medical staffs (n = 157) (%)	*P* value
Age (years)	58.8 ± 15.4	57.7 ± 17.2	31.2 ± 5.2	<0.001 F (2,300): 200.9
Age > 60 years	49 (55.7)	24 (41.4)	0	<0.001 χ^2(2): 107.3[a]
Male gender	49 (55.7)	29 (50)	23 (14.6)	<0.001 χ^2(2):51.7
Weight (kg)	64.6 ± 11	68.0 ± 11.0	71.2 ± 10.1	<0.001 F (2,300): 11.1
Creatinine (mg/dl)	9.05 ± 2.3	2.12 ± 0.6	0.84 ± 0.17	<0.001 F (2,300): 850
GFR (Cauckrof-Gault) (mL/min/1.73 m^2)	13.5 ± 1.3	35.4 ± 12	113.3 ± 20.7	<0.001 F (2,300): 1283
GFR (MDRD) (ml/min/1.73 m^2)	11.9 ± 3.3	32.1 ± 9.9	91.5 ± 21.1	<0.001 F (2,300): 789.2
Anti-HBs levels (mIU/ml)	7.95 (5.1-161)	123 (33.1-540.3)	242 (61.5-313.5)	<0.001 χ^2(2):47.9
Seroconversion rate	39 (44.3)	52 (89.7)	151 (96.2)	<0.001 χ^2(2):95.6
Seroprotection rate	23 (26.1)	32 (55.2)	151 (96.2)	<0.001 χ^2(2): 132.5

HD = Hemodialysis, CKD = Chronic kidney disease, GFR = Glomerolar filtration rate; Values are expressed as Mean ± SD for continuous variables with normal distribution and as median rank (25th75th percentiles) for continuous variables without normal distribution. Categorical variables are expressed as number(percent) Chi-square value(df)

Seroprotection (anti-HBs levels > 100 mIU/ml) occurred in 55.2% of Group-B patients (32 out of 58) and in 26.1% of HD patients (23 out of 88) and 96.2% of Group-C (151 out of 157) (P <0.001).

Univariate analysis

Table 3 shows the comparison data of seroconverters and nonseroconverters.

Out of the 303 vaccinated participants, 44.3% of HD (39 patients), 89.7% of CKD stages 3-4 (52 patients) and 96.2% (151) of participants in the medical staff group were seroconverted [Table 2].

Seroconversion and renal function

When GFR decreased, there was a clear statistically significant decline in seroconversion. This was the case regardless of whether the C-G (not shown) or MDRD formula was used.

Univariate analysis also indicated that the severity of renal function had a significant effect on seroconversion rates. The seroconversion rates for patients with poor renal function were significantly different from those with better renal function, whether calculated by C-G{creatinine clearance <15 ml/min, seroconversion = 39/88, 44%; creatinine clearance = 15-60 ml/min, seroconversion = 52/58, 90% and creatinine clearance >90 ml/min, seroconversion = 151/157, 96% [$\chi^2(2) = 95.6$, $P < 0.001$]} or by MDRD {(eGFR <15 ml/min/1.73 m^2 35/73, 48%; eGFR 15-60 ml/min/1.73 m2 58/76, 76%; and eGFR >90 ml/min/1.73 m2 76/77, 99% [$\chi^2(2) = 66.4$, $P < 0.001$]}.

Table 3 also shows that patients with higher GFR levels had significantly more seroconverters. Univariate analysis also showed that subjects with GFR>90 were 31 times more likely to have seroconversion than subjects with GFR<15 (95%CI: 12.776.9, χ^2:54.3, P<0.001) and the odds of seroconversion for subjects with GFR>90 were three times higher than for those with GFR=15-60 (95%CI: 0.99, χ^2:3.2, P<0.08).

Seroconversion and age

The mean age of the seroconverter group (40.6 ± 16 years) was lower than that of the non-seroconverter group (59.0 ± 17 years). This difference was significant when univariate analysis was used [t (301): 7.8, P <0.001].

Fifty-nine percent of patients in non-seroconverter group were above 60 years compared with 15% of seroconverters [Table 3].

The univariate analysis indicated that individuals under 60 years of age had significantly higher seroconversion (89%) than those above 60 years (51%) [$X^2(1)$:43.2, P <0.001].

Those under 60years were eight times more likely to be seroconverters (95%CI: 4.3-14.8).

Seroconversion and gender

Fifty-three percent of patients in the non-seroconverter group were males, while 29% of seroconverters were males (χ^2:12.6, P<0.001).

Univariate analysis indicated that females had significantly higher seroconversion (85.6%) than males (68.3%) (χ^2:12.0, P=0.001). Females had 2.8 times higher odds for seroconversion compared to males (95%CI: 1.6-4.9).

Multivariable analysis

Logistic regression analysis was used to predict the probability of seroconversion and factors that influenced such a conversion. The predictor variables were the participants' gender, age and three GFR categories.

The model was able to correctly classify 92.6% of those who seroconverted and 50.8% of those who did not, with an overall success rate of 84.2%.

Table 3: Univariate comparison by seroconversion

Variables	Non-seroconversion (n = 61) (%)	Seroconversion (n = 242) (%)	*P* value
Age (years)	59.0 ± 17.5	40.6 ± 16.2	<0.001 t (301):7.8
Age > 60 years	36 (59.0)	37 (15.3)	<0.001 $\chi^2(1)$:50.9
Male gender	32 (52.5)	69 (28.5)	<0.001 $\chi^2(1)$:12.6
Weight (kg)	66.4 ± 11.9	69.3 ± 10.6	0.062 t (301): −1.8
Creatinine (mg/dl)	4.3 ±1.8	1.8 ± 1.7	<0.001t (301): 10.1
GFR (CockcroftGault) (ml/min/1.73 m^2)	14.07 (13.0-14.8)	96.52 (31.8-111.6)	<0.001 Z: 8.9
GFR (MDRD) (ml/min/1.73 m^2)	12.73 (9.9–19.7)	72.68 (31.0-92.3)	<0.001 Z: 8.4
GFR<15 cc/min	49 (80.3)	39 (16.1)	<0.001 $\chi^2(1)$:97.5
GFR>90 cc/min	6 (9.8)	151 (62.4)	<0.001 $\chi^2(1)$:53.9
15≤GFR<60 cc/min	6 (9.8)	52 (21.5)	0.039 $\chi^2(1)$:4.2

HD = Hemodialysis, CKD = Chronic kidney disease, GFR = Glomerolar filtration rate; Values are expressed as Mean±SD for continuous variables with normal distribution and as median ($25^{th}75^{th}$ percentiles) for continuous variables without normal distribution. Categorical variables are expressed as number(percent) Chi-square value(df)

Table 4: Multivariate modeling results for predictors of seroconversion

Variables	Odds ratio	95%CI	Wald (χ^2)	*P* value
Sex (male)	0.88	0.42-1.8	0.11	0.74
Age > 60 years	0.38	0.18-0.84	5.6	0.017
GFR >90cc/min			44.7	<0.001
GFR<15-60 cc/min	0.056	0.2-0.16	28.82	<0.001
GFR <15 cc/min	0.583	0.15-2.1	0.65	0.41
Constant	1.42		59.4	<0.001

Table 4 shows the logistic regression coefficients, Wald test and odds ratio with 95% CI for each of the predictors.

Using a 0.05 criterion of statistical significance, age>60 years and GFR <15 (HD group) had significant partial effects.

Those with the lowest level of kidney function were less likely to seroconvert than those with better kidney function, independent of other factors.

The significant odds ratios for older age, when holding all other variables constant, were found. Inverting the odds ratio for age variable revealed that the under 60-year-old participants were 2.6 times more likely to seroconvert than individuals above 60 years of age (95%CI: 1.2-5.6, χ^2:5.68, *P*= 0.017). Male sex was adjusted for, but was not significant in the model.

Logistic regression with adjusted gender and age showed that the chance for development of seroconversion for the patients with 15<GFR <60 decreased to about 0.95 compared to the subjects with GFR>90. This is while, the rate of development for seroconversion for those with GFR <15 declined to 0.42 compared with subjects with GFR>90.

In Table 4, gender did not show any effect on producing seroconversion.

DISCUSSION

HepatitisB vaccine should be administered to all ESRD patients and healthcare workers in this unit.[26,27] Due to impaired immune system, patients with CKD have a less than optimal response to HB vaccine.[26] The recommended vaccination schedule in dialysis patients is four doses of 40μg, which is twice the normal dosage, at intervals of 0, 1, 2, and 6 months to complete the primary immunization series.[20] To increase the effectiveness of HB vaccine, various methods have been tested, such as recombinant adjuvants, thymopentine, levamisole, zinc, interleukin-2, interferon, erythropoietin, granulocyte-macrophage colony-stimulating factor (GM-CSF), reinforced intramuscular(IM)/intradermal(ID) methods and new vaccines that contain adjuvant, all of which function differently.[28-36]

At present, it is recommended that anti-HBs antibody titers be kept above 100 mIU/ml to induce a protective antibody response in HD patients.[34] Patients who develop anti-HBs ≥100 mIU/ml to HB vaccine should be given a booster dose of vaccine every 5 years. Patients with low level antibody response (anti-HBs ≥10 mIU/ml or <100 mIU/ml) should be given a booster shot after 1 year and every 5 years thereafter.[37]

Until now, there have been no clear data available on the vaccination of patients with CKD stages 3-4, who have a 15 < GFR < 60 ml/min. As it can be seen in the subsequent studies, various dosages, frequencies and methods of administration of HB vaccine in this population have been utilized to develop a protective antibody response.

This study was conducted to determine the efficacy of three doses of 40μg vaccine in stages 3-4 of CKD patients at the time of diagnoses, as compared with the threedoses of 20 μg vaccine schedule given to the normal healthy medical staff and fourdoses of 40μg vaccine schedule given to the HD population. Since responsiveness to HB vaccine in patients with renal disease is reduced, in order to assess a better response, higher dosage of HB vaccine (40μg) was administered.

C. A. M. McNultya and his colleagues compared 20 and 40 μg doses of HB vaccine, administered at 0, 1and 6 months to 121 patients with moderate renal insufficiency. The subjects were at stages 2 and 3 of CKD. Seroconversion was greater (67%) after three doses of 40 μg of vaccine than in patients given a standard dose of 20 μg (57%). However, this was not statistically significant.[37] They showed there was no correlation between the seroconversion rate and severity of CKD.

Gerald DaRoza *et al*. studied 165 patients with GFR<30 ml/min. They vaccinated patients with 40 μg IM at 0, 1, and 6 months. They found an association between the GFR and the seronconversion rate in the subjects.[19]

In our study, seroconversion rates in patients with GFR<15, GFR1560 and GFR>90 ml/min were 44.3%, 89.7%, and 96.2%, respectively. This study showed that the degree of renal impairment has an influence on seroconversion rate.

Siddiqui and colleagues studied the efficacy of four doses of 40 μg vaccine in130 CKD patients as compared to the three-dose 20 μg schedule for the normal population. They found that administering 40 μg vaccine produced a better seroprotection in CKD patients.[38]

Our current study showed 96.2%, 55.2% and 26.1% seroprotection in medical staff, stages 3-4 of CKD and HD groups, respectively.

Fraser *et al*. conducted a study of 68 patients with different severities of renal failure. Patients received four doses of HB vaccine, after which anti-HBs titers were checked at 0, 1, 2, 3, 6, 8 and 12 months. Maximum anti-HBs titers were observed at 8 months. They reported that the degree of renal failure had an effect on the titer of anti-HBs (P <0.002).[39]

In our study, patients with maximum renal failure, those being the HD patients, had less seroconversion (P <0.002) and seroprotection (P <0.002).

In another study, 78 children and adolescents with CKD were given three 20-μg dose course of the HB vaccine.[40] After only two doses of vaccine, seroconversion appeared in all patients. The results showed that a regimen of three 20-μg doses of HB vaccine produced proper immunogenic response in children with CKD. The researchers recommended using three doses of vaccine before the development of ESRD.[40]

Some factors could possibly influence the antibody levels in CKD patients. Older age, male sex, uremia inadequate dialysis, nutritional status, body weight, presence of diabetes, use of low biocompatibility dialysis material, hyperparathyroidism, vitamin D deficiency, anemia, iron overload, serological positivity for Hepatitis-C virus and history of blood transfusion are all the factors that have been reported to induce a poor response to HB vaccine in CKD patients.[7,12,20,34,37,39,41-43]

In our study, age and sex showed an effect in seroconversion rates in univariate analysis. However, in multivariate analysis, there was no significant relationship between sex and seroconversion. In addition, multivariate analysis showed that older patients with the lowest level of kidney function were less likely to seroconvert.

The findings can be summarized as follows Currently, it is not clear whether the different stages of CKD, as well as age and sex could be an independent predictor of seroconversion after administration of HB vaccine. However, our study found that in earlier stages of kidney disease, vaccination is more likely to induce seroconversion compared with the latest stage, which is the dialysis stage. Therefore, kidney function appears to be an independent predictor of seroconversion. In addition, older HD patients appeared to be less likely to seroconvert.

We also found that an increased response rate of 89.7% occurred when 40μg doses of vaccine were used on patients with stages 3-4 of CKD, leading us to conclude that more seroconversion may be obtained in such higher vaccine dosages.

Limitation

Of course, a higher number of CKD patients at stages 3-4 could have further strengthened the results of this study.

CONCLUSION

We suggest that as soon as patients are diagnosed with CKD, they should be administered HB vaccine. We also encourage further studies to assess if higher seroprotection rates could be obtained with administration of higher dosage of vaccine at earlier stages of CKD.

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