Research Article

Prevalence and predictors of non-response to hepatitis B vaccination among dialysis patients

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ABSTRACT

Background: Chronic hepatitis B virus (HBV) infection remains a global health problem and a leading cause of cirrhosis and hepatocellular carcinoma. Dialysis patients have an increased risk of contracting HBV due to shared dialysis machines, use of blood products and arteriovenous fistula or graft needling. The efficacy of HBV vaccination series is reduced in dialysis patients. The efficacy of this intervention needs to be better studied in South Africa.

Methods: All patients undergoing dialysis at a large urban hospital who had received the HBV vaccine at least 6 months prior had the following variables documented: demographics; aetiology of end stage kidney disease (ESKD); mode of dialysis; history of smoking or immunosuppression; body mass index (BMI) and serology (HBV, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) status). The prevalence of non-response to the HBV vaccination and predictors of non-response in these patients was determined.

Results: 129 patients were included with a median age of 45 years, 52.7% were male, 14.3% were HIV positive and 2.3% were HCV infected. 21% of patients had a BMI greater than 30kg/m^2. 8.5% of patients received immunosuppression. The commonest cause of ESKD was 'unknown aetiology' (39.5%) followed by hypertension (31.0%). 55% were receiving haemodialysis and 45% peritoneal dialysis. 21.7% of the cohort had not adequately responded to the HBV vaccine. Immunosuppression was associated with poorer HBV vaccine response ($p = 0.0498$); no other variables predicted seroconversion.

Conclusion: This study from a large urban hospital in Johannesburg, South Africa, demonstrated a seroconversion rate similar to international studies. Only the use of immunosuppression showed a lower odds ratio of a successful vaccination.

Keywords: Hepatitis B Vaccination; Chronic Kidney Disease; Dialysis; Vaccine Nonresponse

INTRODUCTION

More than two billion people worldwide have evidence of past or present Hepatitis B virus (HBV) infection.(1) Approximately 360 million people have chronic HBV infection with a persistently positive Hepatitis B surface Antigen (HBsAg). Each year 600,000 people die from HBV-related acute hepatitis, liver cirrhosis or hepatocellular carcinoma.(2) HBV infection is endemic in South Africa, with 4.8% of males and 3.2% of females testing persistently HBsAg positive.(3) Increased rates are seen in HIV-HBV co-infected communities.(3)

Transmission of HBV occurs through blood and mucous membrane contact.(2) Dialysis patients have an increased risk of contracting HBV due to shared dialysis machines, use of blood products and regular arteriovenous fistula or graft needling. International guidelines recommend that all patients be vaccinated before initiating dialysis.(4) This is a double dose (40 mcg), four-vaccine schedule over six months. Seroconversion is defined as a HBsAb of more than 10 IU/l, which is, therefore, the target for a successful vaccination series.(5) Screening for seroconversion (the presence of HBsAb) is suggested 1–2 months after the vaccine schedule completion, followed by screening every six months to ensure ongoing protection against HBV infection.

HBV vaccination efficacy is known to be reduced in patients with chronic kidney disease (CKD).(6) Older age, elevated body mass index (BMI), underlying chronic illnesses (including diabetes mellitus (DM) and Hepatitis C virus (HCV) infection) and immunosuppression are associated with poorer response to HBV vaccination. Also, patients who do achieve seroconversion after HBV vaccination drop their antibody titres significantly faster than healthy individuals.(7)

Other than vaccination, measures to reduce transmission of HBV infection in dialysis units include performing

dialysis in separate rooms with dedicated machines for HBsAg positive patients, utilising separate trolleys for each patient and strict adherence to universal precautions.(2)

There have been very few studies from Africa that have assessed the seroconversion rate following HBV vaccination in patients undergoing dialysis. Thus, we aimed to assess the rate of seroconversion following HBV vaccination and factors related to non-response to vaccination at a large tertiary care facility in Johannesburg, South Africa.

METHODS

The study was a retrospective cohort analysis of the Hepatitis B status of all dialysis patients at the adult Renal Unit of Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, South Africa. CHBAH is a 2000-bed tertiary care public health facility. All haemodialysis and peritoneal dialysis patients who had received the HBV vaccine at least 6 months prior to September 2018 were included in the study. Exclusion criteria included patients less than 18 years of age, those who had not completed their HBV vaccination series, patients in whom less than two months had elapsed since their final HBV vaccination and patients with HBV infection (acute, previous or chronic infection).

The data collected included: demographic data (age, gender), past medical history of diabetes mellitus (DM), HIV status and CD4 count, history of glomerulonephritis, obstructive uropathy, systemic lupus erythematosus (SLE), cause of end stage kidney disease (ESKD), smoking status, use of immunosuppressive agents, BMI, hepatitis serology results (HBsAg, HBsAb, HBcAb, HCV Ab), and timing of HBV vaccination. Seroconversion was defined as a HBsAb of more than 10 IU/l. The HBV vaccines utilised at this centre were Engerix B produced by GlaxoSmithKline, Heberbiovac HB produced by Macter International (PVT) Ltd or Hep B Vaccine produced by Cipla.

The data was captured in Microsoft Excel and later exported into SPSS (originally, Statistical Package for the Social Sciences and now called Statistical Product and Service Solutions) software where the analysis was conducted.

Continuous variables are expressed as means and standard deviations, or medians and interquartile ranges (IQR), where distributions were normal or non-normal, respectively. Categorical variables are presented as percentages. The odds ratio was calculated for univariate data. The chi-square test of association was used to assess whether there was an association between two categorical variables. Independent samples t-test was used to assess whether the mean value of a continuous variable such as age is significantly related to the outcome. A p value of ≤ 0.05 was considered significant. A logistic regression model was performed to identify possible factors associated with a reduced vaccine response.

Ethical approval for the study was granted by the hospital CEO and University of the Witwatersrand Ethics Committee (Medical).

RESULTS

One hundred and forty patients were receiving haemodialysis or peritoneal dialysis at the time of data collection, of which 11 were excluded from the study. Of the 11 patients, 7 had chronic HBV infection (with a persistently positive HBsAg), 3 had previous HBV infection (all 3 were HBcAb positive, 2 were also HBsAb positive and 1 HBsAb negative), and 1 had recent HBV exposure (HBsAg positive and HBsAb positive but HBcAb negative). The prevalence of chronic HBV infection in our unit was 5%. One hundred and twenty-nine patients, who had received the HBV vaccine at least 6 months prior, were included for further analysis.

Patient characteristics

Of the 129 patients, 71 (55%) were on haemodialysis and 58 (45%) on peritoneal dialysis. 68 (52.7%) patients were male. The median age was 45 years (IQR 33 – 53.3 years). Twenty one percent of the patients had a BMI of greater than 30kg/m^2. The commonest cause of CKD was 'unknown aetiology' (39.5%) followed by hypertension (31%), only 2.3% of the patients had ESKD attributed to diabetes mellitus. 14.3% (18/126) of patients were HIV positive, with a mean CD4 count of 457 ± 237 cells/mm^3. Three (2.3%) patients were HCV-infected. 29.2% (21/72) of patient were smokers. Eleven (8.5%) patients had a history of immunosuppression use, which included a combination of cyclophosphamide, mycophenolate mofetil and/ or tacrolimus. Baseline characteristics according to vaccine status are shown in Table 1.

Vaccine response

All patients completed the double dose (40 μg), 4 vaccine regimen over a 6-month period. One hundred and sixteen patients had available data regarding time to vaccination since starting dialysis, 94 (81%) of these patients started their vaccination schedule within 6 months of dialysis initiation. One hundred and one (78.3%) patients achieved seroconversion, with a documented HBsAb level of >10 IU/l. Twenty-eight (21.7%) patients did not achieve this level and required revaccination.

Factors affecting response to HBV vaccination

Patient demographics, BMI, smoking status, underlying cause of ESKD, HIV or HCV infection, mode of dialysis, timing of HBV vaccination and use of immunosuppression were all assessed for an association with poor response to HBV vaccination. These are listed in Table 2. Logistical regression revealed that the use of immunosuppression had a lower odds ratio (OR 0.181 (95% CI 0.033–0.999, p = 0.0498)) of a successful vaccination and seroconversion.

Table 1. Baseline characteristics according to HBV vaccine status of the patients on dialysis analysed for seroconversion following HBV vaccination

Variable		Total	Outcome	
		(n = 129)	Successfully vaccinated (n = 101)	Revaccination required (n = 28)
Age *(years)*	Mean ± SD	43.0 ± 12.6	42.6 ± 12.4	44.4 ± 13.6
Gender	Male	68 (52.7%)	56 (55.4%)	12 (42.9%)
BMI *(n = 62) (kg/m²)*	<20	7 (11.3%)	7 (14%)	0 (0%)
	20–25	20 (32.3%)	17 (34%)	3 (25%)
	25–30	22 (35.4%)	17 (34%)	5 (41.7%)
	>30	13 (21.0%)	9 (18%)	4 (33.3%)
Smoker *(n = 72)*	Yes	21 (29.2%)	15 (26.8%)	6 (37.5%)
Cause of chronic kidney disease	Hypertension	40 (31%)	31 (30.7%)	9 (32.1%)
	HIV	11 (8.5%)	8 (7.9%)	3 (10.7%)
	Diabetes	3 (2.3%)	3 (3.0%)	0 (0%)
	GN (known)	10 (7.8%)	7 (6.9%)	3 (10.7%)
	Obstructive Uropathy	5 (3.9%)	5 (5.0%)	0 (0%)
	SLE	9 (7%)	8 (7.9%)	1 (3.6%)
	Unknown	51 (39.5%)	39 (38.6%)	12 (42.9%)
eGFR at inception (ml/min/1.73 m²)	Mean ± SD	6.17 ± 4.11	6.15 ± 4.20	6.22 ± 3.85
Mode of dialysis	HD	71 (55%)	52 (51.5%)	19 (67.9%)
	PD	58 (45%)	49 (48.5%)	9 (32.1%)
Time between start of dialysis and vaccination	<6 months	94 (72.9%)	71 (70.3%)	23 (82.1%)
	>6 months	22 (17.1%)	20 (19.8%)	2 (7.1%)
	Unknown	13 (10.1%)	10 (9.9%)	3 (10.7%)
HIV *(n = 126)*	Positive	18 (14.3%)	14 (14.3%)	4 (14.3%)
	Negative	108 (85.7%)	84 (85.7%)	24 (85.7%)
CD4 Count (cell/mm³)	Mean ± SD	457 ± 237	491 ± 251	340 ± 154
Hepatitis C	Positive	3 (2.3%)	1 (1.0%)	2 (7.1%)
Diabetes *(n = 128)*	Yes	4 (3.1%)	3 (3%)	1 (3.6%)
Use of immunosuppressants	Yes	11 (8.5%)	7 (6.9%)	4 (14.3%)
Immunosuppressants drugs used *(n = 8)*	Cyclophosphamide	4 (50%)	4 (100%)	0 (0%)
	Cyclophosphamide and MMF	1 (12.5%)	0 (0%)	1 (100%)
	MMF	2 (25%)	2 (100%)	0 (0%)
	Tacrolimus	1 (12.5%)	0 (0%)	1 (100%)
Completed vaccine series	Yes	129 (100%)	101 (100%)	28 (100%)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; GN, glomerulonephritis; SLE, systemic lupus erythematosus; HD, haemodialysis; PD, peritoneal dialysis

Table 2: Factors associated with reduced HBV vaccine response in the dialysis population

Variable	Odds ratio	95% Confidence Interval	p value
Age	0.098	0.943–1.019	0.303
Male gender	2.072	0.798 – 5.736	0.134
Hypertension	1.224	0.417 – 3.599	0.713
Diabetes	0.673	0.059 – 7.637	0.749
SLE	6.911	0.543 – 87.974	0.136
HIV positive	2.333	0.177 – 30.769	0.520
HCV positive	0.137	0.006 – 3.212	0.217
eGFR at inception	1.011	0.907 – 1.127	0.840
Mode of dialysis	0.476	0.181 – 1.247	0.131
Use of immunosuppressants	0.181	0.033 – 0.999	0.0498

Abbreviations: SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate

DISCUSSION

This is the largest African study assessing vaccination seroconversion among dialysis patients receiving a double-dose, four-vaccine regimen against HBV.

At the time of our study, our unit had a chronic HBV prevalence rate of 5.0%, which is higher than the national average but less than the continental average. A meta-analysis of the prevalence of HBV in African dialysis patients reported the pooled prevalence of HBV at 9.88% (95% CI: 7.20–12.56).(8) The SA Renal Registry annual report of 2020 notes the seropositivity rate for HBV in dialysis patients to be 2.3%.(9) In addition to being at an increased risk of acquiring HBV infection, chronic dialysis patients are more likely to become chronic carriers of HBV than the general population.(8) This makes vaccine protection hugely important.(2)

Of the 129 patients who received the full schedule of HBV vaccination, 101 (78.3%) had seroconverted. Mtingi-Nkonzombi et al. reported vaccine-acquired immunity after their initial vaccination course to be only 23% (25/107) in their dialysis cohort from the Eastern Cape, South Africa. However, most patients (87%) eventually seroconverted after repeated booster dosing.(10) Internationally, reported seroconversion rates are similar to our cohort with 87% seroconversion reported by Siddiqui et al. in India(11); 89% seroconversion reported by Al Saran et al. in Saudi Arabia(12); 83.5% seroconversion reported by Asan et al. in Turkey(13); 70% seroconversion reported by Ferreira et al. in Brazil (14) and 77% seroconversion reported by Cordova et al. in Italy.(15) Lower seroconversion rates are seen in dialysis units administering a three-dose schedule, at 0, 1 and 6 months, at double the standard dose of 20μg (thus 40ug per dose) and in dialysis units administering a four-dose schedule, at 0, 1, 2 and 6 months at a standard dose of 20 μg.(5,7,16,17)

Factors other than vaccine dose and number of vaccinations in the series that have been reported to be associated with poorer vaccine response include older age, elevated BMI and underlying chronic illnesses (DM, HCV infection), delayed HBV vaccination, and immunosuppression.(4)

Lower seroconversion rates are noted in older dialysis patients following HBV vaccine. The reduction in HBV vaccine efficacy has been postulated to be due to age-related immunosenescence.(4,7,15,16) Zitt et al. (7) from Austria reported a mean age in non-responders of 66.5 ± 12.5 years vs seroconverters of 60.2 ± 15.1 years ($p < 0.001$) and Patel et al. in the USA reported age ≥ 58 years was independently associated with nonresponse (adjusted relative risk (ARR), 1.62, 95% CI 1.06–2.46; $p = 0.02$).(16) An Italian study by Cordova et al. demonstrated a decrease in HBV vaccine efficacy as their patients aged (40% seroconverted in the 61–70-year age group but only 14% in the 71–80 year age group).(15) Our cohort had a median age of 45 years (IQR 33–53.3 years), with only a small subset of patients (10.9%) above the age of 60 years, possibly explaining our non-significant finding in age affecting seroconversion.

A poor HBV vaccine response in patients with an elevated BMI has been attributed to obesity-related immune modulation, possible insufficient vaccine dose for weight, or the suboptimal vaccine needle length to deliver adequate penetration for intramuscular delivery.(16) Patel et al. reported a BMI ≥36.4 kg/m^2 as a variable independently associated with nonresponse, with 14/15 patients with a BMI ≥36.4 kg/m^2 requiring revaccination.(16) In our cohort, 21% (16/62) of patients had a BMI > 30 kg/m^2, and none had a BMI >35kg/m^2.

HCV infection and underlying DM have been associated with lower HBV vaccination seroconversion rates. HCV infection potentially causes impaired liver function, resulting in reduced immunity.(14) A Brazilian study by Ferreira et al. demonstrated that the absence of HCV infection was independently associated with HBV vaccination seroconversion (OR = 5.239, 95% CI:1.279–21.459, p = 0.021).(14) South Africa has a very low rate of HCV infection, which was mirrored in our cohort.

Internationally DM is a leading cause of ESKD and comorbidity in patients on dialysis.(18) Zitt et al. detailed a baseline prevalence of DM in their dialysis cohort of 39.2% (167/427), and in this study, patients with DM were less likely to seroconvert following HBV vaccination (p = 0.04).(7) Taheri et al. reported that dialysis patients with DM were 4.38 times more likely to require revaccination than those without DM (p = 0.002).(19) Patients with ESKD attributable to longstanding DM often have other end-organ disease, which often precludes them from kidney transplantation. As eligibility for transplantation is required for dialysis in the South African public health program, this underscores why the current study only had 2.3% of patients with DM.

Seroconversion after HBV vaccination is reduced as kidney failure progresses.(4,19) Guidelines thus recommend that patients with CKD be vaccinated as early as possible during their kidney disease, preferably prior to initiation of dialysis.(4,20) Eighty-one percent (94/116 patients with data) of our cohort were vaccinated within the first 6 months of starting dialysis, which may have contributed to our high vaccine response rates.

Antigen-specific B and T cells, along with cytokines (tumor necrosis factor (TNF)-α and interleukins (IL) 1β, 6, and 12), play an important role in the immune response to HBV vaccination, allowing for seroconversion.(21,22) Solay et al. demonstrated reduced efficacy of the HBV vaccine in patients who were exposed to TNF-α blockade.(23) This is in keeping with our study results, in that immunosuppressive medication was associated with a significantly lower seroconversion rate following HBV vaccination.

A meta-analysis including 1821 HIV positive participants showed those with higher CD4+ T-cell counts had a more robust response to HBV vaccination than those with low CD4+ T-cell counts, especially those with a baseline CD4+ T-cell count >500 cells/mm^3 (p < 0.001).(24) The HIV status was known in 126 patients in our cohort. Of these 18 (14.3%) were HIV positive with a mean CD4 count of more than 450 cells/mm^3, which probably accounts for the lack of association between HIV status and poor HBV vaccination response in our study.

Our study found no significant difference in HBV vaccination seroconversion rates between patients undergoing haemodialysis and peritoneal dialysis. This is in keeping with the findings from many other studies revealing no differences in HBV vaccination seroconversion rates according to the mode of dialysis.(5,7,11,13)

Limitations: Limitations of this study include the retrospective nature of the study, resulting in some missing data, including parameters that may be associated with poor HBV vaccine response such as C-reactive protein, dialysis adequacy, residual diuresis, or dialysis vintage. There were small patient numbers in some of the subgroups, which may have limited our ability to demonstrate statistical significance in vaccine unresponsiveness. As this was a single-center study, the results may not be generalizable to all ESKD patients.

CONCLUSION

Patients on dialysis are at increased risk of contracting HBV infection. This risk can be reduced by HBV vaccination and regular monitoring of HBsAb titres to readily administer booster doses as the levels wane. The study demonstrated high levels of seroconversion following the HBV vaccine series (40 μg for four doses). Larger studies are however required to further investigate factors contributing to poorer vaccine response.

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