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Hepatitis B Vaccination Status in Children with Chronic Kidney Disease

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Abstract

Context

Increased risk of acquiring Hepatitis B virus infection in these patients because of increased exposure to blood products, shared hemodialysis (HD) equipment, breaching of skin, frequent injections and immunodeficiency are most possible reasons.

Aims

This study aimed to see the status of hepatitis B vaccination among children with CKD & to see the factors associated with non-responders.

Materials and Methods

This cross-sectional study was carried out in the Department of Pediatric Nephrology, Bangladesh Institute of Child Health and Dhaka Shishu (children) Hospital, from July 2018 to Dec 2019. A total of 36 previously diagnosed advanced stages of CKD patients were enrolled in the study.

Results

A total of 36 CKD patients were included in the study, 55.55% (n=20) were male and 44.44% (n=16) were female. The mean age and duration of CKD were 8.57±0.59 years and 1.54±0.26 years respectively. 100 % of patients were vaccinated for hepatitis B and the infection rate was 0%. There was a significantly lower seroprotection rate when compared with the seroconversion rate. The male gender had a significant chance of decreased immunogenicity concerning the vaccine against HB, while the female showed a better response.

Conclusion

Periodic monitoring of antibody titer and secondary vaccination should be recommended to obtain a higher seroprotection level.

Keywords: Chronic Kidney Disease, Hepatitis B Vaccination, Seroconversion Rate

Introduction

Hepatitis B virus (HBV) infection is a global health problem nowadays and affects about 350-400 million people worldwide. The prevalence of HBV infection is highest in the WHO Western Pacific Region and the WHO African Region [1]. In Bangladesh, HBV prevalence is indeed currently lower than it used to be 0% to 4.9% in the past five years, compared to 7.8% in the early 1980s. The prevalence among multi-transfused children attending BSMMU is 3% and in adults is 6.5% [2].

Chronic kidney disease patients are mostly immune compromised and more prone to infections, especially those requiring hemodialysis [3]. Increased risk of acquiring HBV infection in these patients because of increased exposure to blood products, shared hemodialysis (HD) equipment, breaching of skin, frequent injections, and immunodeficiency are the most possible reasons [4].

Hepatitis B infection can be effectively prevented by vaccination [5]. In Bangladesh, a mass vaccination program against HBV was introduced in the EPI schedule in 2003 which covers more than 97%. Compared to a response rate of over 90% in the general population, only 50 to 85% of dialysis patients achieve protection level antibodies [>10IU/L] following HB vaccination [6]. Routine vaccinations of patients, and healthcare workers has dramatically reduced the prevalence of HBV infection in hemodialysis patients [7, 8]. Hepatitis B vaccination is recommended for all children with chronic kidney disease [9]. It is advised that these patients should be vaccinated at an earlier stage as the response is good with higher eGFR [10]. Despite strong recommendations, only 46% of dialysis units were routinely practicing to immunize the patients according to the Renal association's recommendations in the United Kingdom [11].

Very little data is available regarding the hepatitis B vaccination status and response rate of primary hepatitis B vaccine of Bangladeshi children with CKD, so this study is aimed to see the status of hepatitis B vaccination among children with CKD & to see the factors associated with non-responder.

Methods

This cross-sectional, observational study was conducted at the Department of Pediatric Nephrology and Hemodialysis Center of Dhaka Shishu (children) Hospital and Bangladesh Institute of Child Health, from July 2018 to Dec 2019. All CKD patients (6 months-18 year) admitted or visited in(OPD) of Dhaka Shishu hospital, were included in the study. CKD was defined as GFR ≤ 60ml/min/1.73 m² over a period of more than three months [10]. Patients who were being recently vaccinated after diagnosis of CKD, with history of previous hepatitis C infection, those taking immunosuppressive medication were excluded from the study. Then an elaborate history was taken and clinical characteristics of the patients including gender, age, height, weight, underlying disease, duration & frequency of hemodialysis per week were recorded on a specially designed pro-forma.

Before enrollment, patients were tested for HBs Ag at virology laboratory by Abbott Architect i2000SR/Vitros ECi System (J&J) Siemens Advia Centaur XP Random Access Multi-batch Immunoassay Analyzer.

Immunogenicity or antibody response to the vaccine were determined by measuring anti-HBs titers. Anti-HBs titer was estimated in the serum sample by Abbott Architect i2000SR/Vitros ECi System (J&J) Siemens Advia centaur XP Random Access Multi-batch Immunoassay Analyzer. Anti-HBs titers are expressed in mIU/mL. Serum anti-HBs level ≥ 10 mIU/mL was considered as seroconversion, while those with levels > 100 mIU/mL were considered as high immune responders or seroprotection [12]. The other medical records were analyzed to correlate the response to vaccine with several clinical and biological factors.

Statistical analysis was compiled by SPSS version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The quantitative observations were indicated by frequencies and percentages. Fisher's exact test was used for categorical variables, Kruskal-wallis test & unpaired t-test were used for continuous variables. A P value <0.05 is considered as statistically significant.

Informed written consent was taken from each patient or legal guardian and assent was taken who were over 7 year old. The consent form clearly described the purpose and methods of study, confidentiality of the interview, risks and benefits of participation in the study, their rights to participate voluntarily and to refuse at any point of time without consequences. Approval in this regard was taken from institutional ethical review committee.

Results

Table 1: Demographic, clinical and laboratory characteristics of patients with different stages of CKD enrolled in the study (n=36)

Variable	MHD (n=18)	Stage- 3-4 (n=12)	Stage-5 (n=6)	P-value
Age in years	9.055556± 3.09596	8.383333± 4.29584	7.5± 3.619392	[a]0.7335
Male gender, n (%)	9(50%)	8(66.67%)	3(50%)	[b]0.663
Duration of CKD (year)	1.625± 1.475327	1.486111± 1.399769	1.558333± 2.280442	[a] 0.5477
Mean height (cm)	119.7777± 13.09596	106.0895± 15.991	108.0895± 13.991	[a] 0.004[s]
Mean weight (Kg)	20.5833±7.532	16.33±8.473	17.33±6.474	[a] 0.902
Mean BMI(Kg/m²)	14.06315± 3.175357	13.57± 2.11	13.487±1.998	[a] 0.9603
Hypertension (Yes)	12(66.67%)	1(8.33%)	4(66.67%)	[b] 0.003 [s]
Mean SBP (mm of Hg)	123.8888± 25.2334	108.3333± 20.7772	110.3333± 21.7672	[a] 0.048 [s]
Mean DBP (mm of Hg)	80.0500± 20.0066	69.4444± 10.6667	72.4123± 12.6567	[a] 0.083
Creatinine (mg/dl)	4.826667± 0.9656391	2.415± 0.4271151	5.283333± 3.548756	[a] 0.0001 [s]
Bl.Urea (mg/dl)	51.48459± 20.57074	45.68161± 21.08194	77.26424± 21.9515	[a] 0.0088 [s]
S. Calcium (mmol/L)	2.072222± 0.332204	2.058333± 0.2574643	2.943333± 2.132057	[a] 0.6817
S. Inorganic Phosphate (mmol/L)	2.472222± 1.347244	2.366667± 1.290055	3.565± 0.9506577	[a] 0.0384 [s]
Hb% (g/dl)	9.394444± 1.865309	9.641667± 1.239104	9.216667± 1.706947	[a] 0.9319
Albumin (gm/L)	24.88889± 8.322251	27.55± 5.909238	25.88333± 3.123726	[a] 0.6246
SGPT (U/ml)	33.83333± 30.99763	26.41667± 7.403419	39.83333± 53.11654	[a] 0.3272
PTH (pg/ml)	895.9611± 714.7617	689.975± 666.1052	792.7333± 347.1616	[a] 0.3152

Results were expressed as Mean ± SD, s= significant

[a]P-value reached from Kruskal wallis test and [b] P-value reached from Fisher's exact test

p-value <0.05 = significant

Table 1 shows the clinical and biochemical characteristics of study patients. Kruskal wallis test was done to measure the level of significance. Statistically significant high mean height was found in MHD group when compared to non-dialysis group (p=0.004) Mean systolic blood pressure was significantly higher in MHD group compared to non-dialysis group (P= 0.048). Serum creatinine, blood urea and serum inorganic phosphate was significantly high in stage 5 non-dialysis stage when compared to stage 3,4 and MHD group (p=<0.05).

Table 2 shows 100 % patients were vaccinated for hepatitis B and infection rate 0%. Mean anti-HBs titer within seroconversion level but seroconversion rate was only 38%. Seroprotection rate was only 8.3%. Sixty one percent patients did not achieve seroconversion.

Table 2: Hepatitis B vaccine status of study population (n= 36)

Variables	No (%)
Vaccination status (yes)	36 (100%)
HBsAg status (negative)	36 (100%)
Mean Anti-HBs level (mIU/ml)	29.81 ±20.02
Seroconversion rate	14 (38%)
Seroprotection rate	3 (8.3%)
Non-seroconversion	22 (61%)

Values expressed as Means ± SD and numbers (percentage)

Table 3: Comparison of Anti-HBs titer among different stages of CKD patient (n=36)

Anti- HBs titer (mIU/mL)	MHD (n=18)		Stage 3-4 (n=12)		Stage 5 (n=6)		Total (n=36)	p-value
	N	%	N	%	N	%	N (%)	
0-10 (Non-seroconversion)	11	61%	6	50%	5	83%	22 (61%)	*0.718
>10-100 (Seroconversion)	6	33%	4	33%	1	17%	11 (30.5%)	
>100 (Seroprotection)	1	6%	2	17%	0	0%	3 (8.3%)	
Total	18	100%	12	100%	6	100%	36	

Values expressed as numbers & percentage
[b] P-value reached from Fisher's exact test
p-value <0.05 = significant

Table 4: Comparison between seroconversion and seroprotection rate of study population (n=14)

	Group	Mean Anti-HBs (mIU/mL)	Std. Err.	Std. Dev.	[95% Conf.	Interval]	P-value
Sero conversion	11	30.76385	7.673725	18.42714	15.26229	46.26146	<0.001
Sero protection	3	247.81	21.17261	36.67204	156.7116	338.9084	
Combined	14	71.14931	8.1298	95.11813	10.994921	131.1537	
Difference		-217.0562	22.27394		-261.5934	-172.6589	

Results were expressed as Mean, standard error, SD, 95% confidence interval. s= significant
P- value reached from t-test and p-value <0.05 = significant

Table 5: Univariate and multivariate modeling results to predict the factors that influenced seroconversion in the study population(n=36)

	Univariate analysis			Multivariate analysis		
Variables	Odds Ratio	95% CI	P-value	Odds Ratio	95% CI	P-value
Males (Gender)	0.27	0.06-1.07	0.062	0.18	0.04-0.90	0.038[s]
Age						
<5 year						
5-10 year	0.57	0.09-3.81	0.567	0.48	0.06-3.64	0.475
11-18 year	0.57	0.08-4.29	0.587	0.58	0.07-4.91	0.615
GFR category						
GFR<15 vs ≥15-60	2.00	0.49-8.13	0.327	2.77	0.55-14.03	0.227

GFR = Glomerular filtration rate
S = significant
An odds ratio with 95% CI were done for each of the predictors.
P-value <0.05 =significant.

Table 3 shows the seroconversion and seroprotection level in different stage of CKD patients. Fisher's exact test was done to measure the level of significance. There was no statistically significant difference among the groups.

Table 4 shows the comparison between seroconversion and seroprotection group among study population. T- test was done to measure the level of significance. There was significantly lower seroprotection rate when compared with seroconversion rate.

Table 5 shows univariate and multivariate logistic regression analysis to predict the probability of seroconversion and factors that influenced non-seroconversion. These results show Odds for males 74% less chance of having seroconversion than non-seroconversion females which was statistically significant. In the case of GFR, Univariate analysis showed that subjects having GFR >15-60 were 2 times more likely to have seroconversion than subjects with GFR <15 but this was statistically not significant (P=0.227)**.**

Discussion

Chronic Kidney Disease patients are prone to various infections including hepatitis B virus infection as the result of impaired immune responses. So, preventive measures are important to reduce the prevalence of hepatitis B infection. Limited data are available regarding the hepatitis B status and response rate of the primary hepatitis B vaccine of Bangladeshi children with CKD, so this study aims to see the status of the hepatitis B vaccine among children with CKD patients & to see the factors associated with non-responders. This study will help us to see the status of hepatitis B in children with CKD population which will help us about prevention and treatment of hepatitis B infection.

This study showed that the infection rate of hepatitis B among children with CKD was 0% and 100% of patients were vaccinated against HBV through EPI schedule. Johnson *et al*. reported the prevalence of hepatitis B surface antigen (HBs Ag) positivity ranged between 1.3% and 14.6% which is not consistent with this study [13]. However an analysis of data from the Dialysis Outcome and Practice Pattern study showed similar results [14]. Seroconversion (anti-HBs >10 mIU/ml) was seen in only 38% of the study population with CKD. This is in contrast to 95% seroconversion known in the normal population [15]. Kohler *et al*. also found similar findings [16]. This emphasizes the need for checking antibody titers following immunization in children with CKD as seroconversion may not happen. In this study seroprotection (anti-HBs >100 mIU/ml) was seen in only 8.3% of the CKD children whereas 90-95% seroprotection is expected in the normal population which is nearly the same to another study [17].

In this study, the mean peak anti-HBs titer was 29.81 ±20.02 mIU/mL. Fabrizi *et al*. demonstrated a similar study and found similar findings with a conventional HB vaccine but anti-HBs geometric mean antibody concentration was 9-fold higher in an adjuvant HB vaccine group [18]. This result also emphasizes that higher doses or an accelerated vaccination schedule may be needed.

In this present study vaccine response rate were compared among different stages of CKD patients and found no

difference in immune response to HB vaccine which is similar to other study [19]. Kamath *et al*. showed no difference in the seroconversion rates between children who were on dialysis and children with CKD stages II to IV [20]. These results were consistent with this study.

This study result showed that there was significantly lower seroprotection rate when compared with seroconversion rate which is consistent with other study [17]. So we need to follow up the persistence of anti-HBs antibody titer in a protection level & Buti *et al*. also showed that in 41% of responsive patients the levels are undetectable at three years [21]. Kong *et al* recommend that anti-HBs antibody titers should be kept above 100 mIU/ml to induce a protective antibody response in HD patients [22]. McNulty *et al* reported that 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 antibody level (anti-HBs ≥10 mIU/ml or < 100 mIU/ml) should be given a booster shot after 1 year and 5 years thereafter [23].

In current study it was observed that patients with GFR levels >15-60 ml/min/1.73m² had 2 times more likely to have seroconversion than patients with GFR < 15ml/min/1.73m², but statistically not significant. Other study also showed similar findings [10, 19, 24].

This present study showed male gender had significant chance of decreased immunogenicity concerning the vaccine against HB, but female showed better response which is consistent with other study [19, 25]. Trevisan *et al* showed that gender affects the immune response to HBV vaccine, particularly evident in the cases of females vaccinated after one year of age who exhibited a statistically significant increase in median antibody titer with respect to males [26]. At the moment, the only plausible explanation of this evidence could be that if innate immunity is more or less the same in both gender, adaptive immunity is more pronounced in females. Klein *et al*. reported that innate and adaptive immune responses to vaccination exhibit relevant gender-related differences [27]. Hannah *et al*. said that Genes for toll-like receptor pathway and type 1 interferon induction justifies these differences because of several genes that are immune-related are located on the X chromosome and play a pivotal role in immune competence [28].

In this study there were no statistically significant differences in terms of age, gender, BMI, and other biochemical parameters between dialysis and non-dialysis group but on MHD group patients were more hypertensive compared to non-dialysis group. Other study also found similar findings [29, 30]. The findings can be summarized as follows currently, it is not clear whether the different stages of CKD, as well as gender could be an independent predictor of better seroprotection after administration of HB vaccine. However, this study found that HB vaccine recipients with CKD were less likely to induce seroconversion and seroprotection and degree of renal impairment might have an influence on seroconversion rate. Therefore, dialysis appears to be an independent predictor of seroprotection.

This study had some limitations. The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not reflect the exact picture of the entire community.

Conclusion

It may be concluded that vaccination status of chronic kidney disease in children against hepatitis B virus was satisfactory but seroconversion rate and antibody titers are low following primary vaccination schedule. The frequency of HBV infection is low among children with CKD but should not be neglected. Numerous host factors like lower GFR and male gender may play a role in the reduced response to HBV vaccine.

From this study we can recommend that Antibody titers should be monitored periodically and maintenance of anti-HBs titer in a seroprotection level by secondary vaccination should be recommended.

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