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The Immune Response after Double Dose Hepatitis B Vaccination in Hemodialysis Patients: Influence of Age and Hepatitis C Virus

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ABSTRACT

Objective: To determine the efficacy of Hepatitis B vaccination among the candidates of maintenance hemodialysis due to chronic kidney disease and to measure the impact of ageing and Hepatitis C infection upon immune seroconversion.

Study Design: Cross-sectional study.

Place and Duration of Study: Nephrology Department, Multan Institute of Kidney Diseases (MIKD), Multan Pakistan from Jan to Jun 2020.

Methodology: Two hundred male and female patients diagnosed with end-stage kidney disease on maintenance dialysis (more than three months) with the range of age, 15 to 70 years, were selected by non-probability consecutive sampling. Already treated patients of HB virus and those with HB virus detectable by ELISA were excluded from the study. Data was accessed through hospital management software records. Three months after the three or four completed doses, antiHBs titer was assessed by ELISA. Cut off the value of anti-Hbs titer was 10U/L to differentiate between responders and non-responders of HBV.

Results: Among the 117 responders, 109 (93%) cases received four double doses of the vaccine, while only 8 (7%) were those who received three double doses. Among 83 non-responders, 52 (63%) were above age 40 years, while 31 (37%) were of age 40 years or below. In addition, among the non-responders, 63 (76%) were Hep C positive, while 20 (24%) were Hep C negative patients.

Conclusions: Four double-dose vaccines have been effective for haemodialysis patients with end-stage kidney disease. Vaccine response is inversely correlated with age and Hepatitis C virus.

Keywords: End stage kidney disease, Haemodialysis, Hepatitis B virus, Hepatitis C virus & vaccination response.

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INTRODUCTION

Chronic kidney disease (CKD) is the functional impairment of kidneys that gradually worsens over a while. There has been approximately a 40% rise in the mortality rate attributed to this non-communicable disease in the last three decades.[1] Just recently, government health agencies marked CKD as a global health problem and realized that they must play a role in devising and implementing strategies for its effective management at a larger scale as this issue is now beyond the capability of individual organizations.[2] Simply calculating the estimated glomerular filtration rate by measuring urine proteins and serum creatinine has been recommended for mass screening programs for CKD.[3] However, in developing countries, because of the high cost of treatment, lack of resources and poor management, this disease rapidly advances to end-stage kidney disease (ESKD).

CKD is a progressive disease that compromises the quality of life and life expectancy. Moreover, it may worsen because of several factors, including autoimmune diseases, electrolyte imbalance, recurrent stones and comorbidities, especially hypertension and diabetes mellitus. Hence, a multidimensional approach comprising public awareness, institutional support and individual training has to be adopted to achieve the set goals. In addition, CKD patients are predisposed to opportunistic infections, bone diseases, cardiovascular accidents, cognitive impairment and acute tubular necrosis. Therefore, each worsening factor has to be countered by lifestyle modification, nutritional restrictions, salt and mineral adjustment, deficiency replacements (e.g., Haemoglobin) and optimizing hypertension and diabetes mellitus.[4]

Rapid deterioration of the immune system in patients with CKD has been attributed to solute retention (uraemia) and metabolic dysfunction related to vitamin D and calcium deficiency. Together these factors halt the maturation, activation and functioning of immune cells, including monocytes and macrophages.[5] Compromised immunity justifies vaccinating CKD

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patients against vulnerable and contagious infections, but due to the lack of randomized control trials (RCTs), no clear guidelines are available proportionate to the indigenous epidemiological needs. Depressed immunity intensifies the morbidity and mortality related to CKD; hence must not be ignored and must be the focus of research so that ways and means can be explored to minimize the CKD-related compromised quality and quantity of life.[6]

CKD patients on hemodialysis (HD) are additionally exposed to blood-borne viral diseases, especially Hepatitis B (HB). This is a challenging issue, as a regular vaccination regime has been found inadequate and non-effective. Failure to maintain seroresponse after HB vaccination (HBV) in HD patients has been investigated and attributed to inherited and acquired factors such as sex, age, diabetes, hypertension, uremic state and nutritional status.[7] For achieving and maintaining optimal seroconversion levels, investiga-tors have been working on various interventions, including; increasing the amount and frequency of HBV, modifying the vaccine and adding various adjuvants. All these solutions have been found effective to a variable extent and are still under trial.[8]

Mulley *et al.* reviewed the RCTs destined to explore the efficacy of double dose HBV in CKD patients, which was only effective in patients on HD, and the conclusion was not in favour of double dose HBV, possibly due to insufficient data.[9]

The burden of kidney diseases in developing countries is alarming due to a lack of resources, awareness and increasingly prevalent comorbidities. Preventing haemodialysis patients from blood-borne contagious diseases is a challenging and essential goal of disease management. In our part of the world, the published data about the statistics of CKD and its management is very limited. The present study has been designed to investigate the efficacy of double-dose HBV by calculating serum anti-HBs titer in HD patients with different categories of dose frequency, age groups, Hepatitis C status and liver enlargement.

METHODOLOGY

This cross-sectional study was conducted at Nephrology Department, Multan Institute of Kidney Diseases (MIKD), Multan Pakistan, from January to June 2020 after approval by the Institutional Review Board of Indus Hospital, Multan (IRD-IRB-2019-11-004).

The sample size was calculated using WHO software, taking the proportion of excellent response equal to 48.5%, confidence level equal to 95% and margin of error equal to 7%.[10] A total of 200 male and female patients suffering from ESKD on maintenance HD for more than three months were selected by non-probability consecutive sampling.

Inclusion Criteria: Male and female patients, of age range 15 to 70 years, diagnosed with end-stage kidney disease on maintenance dialysis (more than three months) were included in the study.

Exclusion Criteria: Patients who had previously got the antiviral treatment of HB virus and now HB virus negative by Polymerase chain reaction (PCR) test and patients who were HB virus positive by Enzyme-linked immunoassay (ELISA) and negative by PCR were excluded from the study.

After informed written consent, data of all patients from "Hospital Management Information System" software was retrieved regarding Hepatitis B and C viral status, HB vaccination status and liver size. Liver size more than 16 cm on ultrasound was considered as enlarged.[11]

As per hospital protocol, all the patients were given 40 micrograms of HB vaccine (double dose) as a first dose, then a second dose on day-30, followed by the third dose on day-60, while the last dose was given six months after the first dose. The patients who had completed three doses during data collection were also included in the study. Three months after the completion of the last dose, the anti-Hbs titer was measured through ELISA at the MIKD laboratory. Cut off the value of the anti-Hbs titer was 10U/L to differentiate between responders and non-responders of HBV.[12]

Statistical Package for Social Sciences (SPSS) version 22.0 was used for the data analysis. Frequency and percentages were calculated for the qualitative variables. The p-value of ≤ 0.05 was considered statistically significant, determined by the chi-square test.

RESULTS

The study sample of 200 CKD patients had a 58% (116) male population and 42% (84) female population, while the patients above and below the age of 40 were almost equal. A comparison of HBV response against the dose frequency, Age group, Hep C viral status and liver status has been shown in the Table, while the percentages have been presented in the Figure.

DISCUSSION

The prevalence of CKD among the Pakistani population above the age of 40 years has been estimated at 12.5%, which is alarming and stresses disease prevention and management initiatives at the primary care level.[13]

Table: Frequency of Demographic and Clinical Characteristics of study Participants with Antibody Titer Response (n=200)

Characteristics		Antibody Titer Response n(%)		
		Non-Responder (n=83)	Responder (n=117)	*p*-value
Vaccination	4 Dose	40 (48)	109 (93)	<0.01
	3 Dose	43 (52)	8 (7)	
Age group	<=40 years	31 (37)	67 (57)	<0.01
	>40 years	52 (63)	50 (43)	
Hepatitis C Virus	C +ve	63 (76)	56 (48)	<0.01
	C-ve	20 (24)	61 (52)	
Liver	Normal	65 (78)	79 (68)	0.094
	Enlarged	18 (22)	38 (32)	

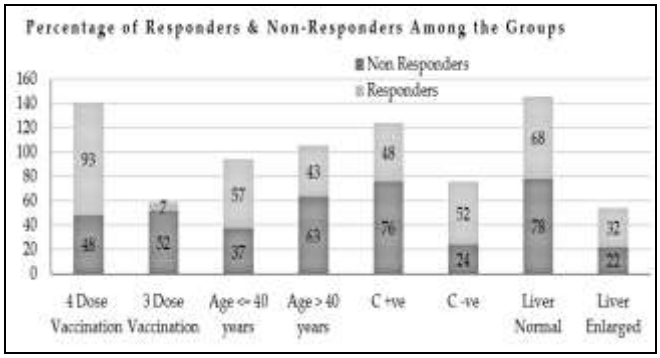

Figure: Percentage of Responders & Non-Responders among the groups (n=200)

93% of patients receiving four doses of vaccine had an effective response, while only 7% of patients receiving three doses had a similar response after three months of the last dose. This difference was statistically significant, meaning that four doses regime is superior to three doses. In contrast to our study, Ayub *et al*. documented against our finding that a double dose regime of the vaccine on days 0, 30, 60 and 180 did not improve immunity and antibody titer fell below 10 mIU/mL gradually over six months.[14] This disparity may be because most of the non-responders were suffering from comorbidities like diabetes and hypertension. Furthermore, it was stated that those having initial high antibody titer (above 1000 mIU/mL) did not show a decline in antibody titer level. Kamath *et al.* investigated the efficacy of a regular dose vaccine among children suffering from CKD and concluded their findings with the recommendation that a regular three doses regime is insufficient. Antibody titer must be monitored regularly as the immunity fades out faster in CKD patients.[15] da Silva *et al*. and Grzegorzewska *et al.* also documented poorer seroprotection after twelve months with regular three doses of HBV in CKD patients than with four double dose regimes.[16,17] Fabrizi *et al*. recently authenticated the efficacy of four double dose regimes by monitoring the antibody titer levels for up to fifty months.[18]

Our results showed that a significantly higher number of non-responders (63%) belong to the age group above 40 years, while only 37% of patients below 40 years of age were non-responders. Hence, our results indicate that the impact of HBV diminishes with age. Recently Dimitrov *et al*. investigated the variables affecting the success of the same HBV regime through the Bayesian statistical model and concluded that age is the most relevant inversely proportional factor.[12] da Silva *et al*. also explored the serological and cellular responses against HBV in young and elderly patients on maintenance dialysis. Specifically, CD4 + T cells' deficiency was found to be responsible for compromised immunity, and this correlation in old age was independent of CKD. Their study concluded that vaccine inefficacy could be resolved by increasing the dose and frequency of HBV.[16] The underlying mechanism has been related to the fact that ageing leads to immunosenescence due to the inability of immune machinery to recognize self-antigens and inadequacy to defend against foreign invaders owing to undermined innate and humoral responses.[19]

Non-significantly higher percentages of responders and non-responders were observed in patients with normal liver than in patients with an enlarged liver. However, this was not conclusive, possibly because in our sample, most cases had normal liver size with non-compromised functioning, and even the enlarged liver is not essentially inefficient.

According to our results, 76% of Hepatitis C positive patients failed to respond to HBV, while in the case of Hepatitis C negative patients, the non-responders were only 24%, and the difference was statistically significant. This shows that Hepatitis C infection is inversely correlated with HBV response.

Navaro *et al.* also documented similar results that Hepatitis C-positive patients could not attain an optimal seroconversion with three double doses of HB.[20] Remarkably, Almueilo *et al.* concluded that the effect of Hepatitis C status upon response to HBV in

chronic HD patients is non-significant. This contradiction may be explained by the difference in methodology, as in this study, antibody titer was calculated only six weeks after the last dose, and in the present study, the same levels were calculated three months after the last dose.[11] Saco *et al.* reviewed the published research data and stated that HBV response is poorer in Hepatitis-C patients and even worse in patients with cirrhotic liver. The underlying pathological mechanism is related to deficiency of programmed death 1 (PD-1) receptors, whose concentration is inversely correlated with immune cells (T & B lymphocytes) activation.[21]

Recently Shi *et al*. probed the molecular mechanisms involved in HBV seroprotection failure among Hep C positive chronic HD patients and reported that it is the exaggerated expression of inhibitory receptors (killer cell lectin-like receptor subfamily G member 1) KLRG1 that hinders the normal functioning of CD4 + T cells and halts the physiological immune response in such patients.[22]

CONCLUSION

Our study has determined the factors that may enhance or suppress the HBV response among the local cohort of ESKD cases. Four double doses of HBV lead to a sustained and effective immune response in these highly vulnerable HD patients. However, in the case of elderly age and HCV-infected cases, the immune response is compromised, and strict and regular monitoring through antiHBs titers is recommended.

Conflict of Interest: None.

Author's Contribution

MRA: Conception, writing, statistical analysis, supervision, interpretation of data, TA: Interpretation of data, critical review and analysis, KB: Data collection, writing, analysis, NH: Statistical analysis, critical review interpretation of data, SA: Data collection , writing.

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