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Immunological Response to Hepatitis B Vaccine in End Stage Renal Diseases

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Abstract

Background End stage renal diseases patients have lower seroconversion rates compared with the subjects with intact renal function. Moreover, even after the completion of vaccination schedule anti-hepatitis B titers of responder who kept on dialysis, patients are low and decline logarithmically with time.

Objectives To determine the response of patients with end stage renal disease undergone hemodialysis to hepatitis B virus vaccination and to identify the factors that could affect this response.

Methods One hundred patients with an age range from 21 to 75 years complaining of chronic renal failure on regular hemodialysis. Patients negative for hepatitis B antigen and anti-hepatitis C were vaccinated with 40µg of Euvax B intramuscularly in the deltoid muscle by following a schedule of 0, 1 and 2 months. The antibody titer was tested at third month and if titer was <10 or 10-100IU/mL (patients whom regarded as non-responded or poor responded). Then they were given another fourth dose (40µg) of vaccine at sixth month.

Results The rate of seroconversion to hepatitis B vaccine among individuals with end stage renal disease is 63%. Thirty one (31%) patients were anti hepatitis C virus positive. Eighteen (58%) were responsive to hepatitis B vaccination and 13 (42%) did not response to Hepatitis B vaccination. Advanced age, sex and diabetes mellitus show no effect on response to vaccination. The response to hepatitis B vaccine is significant in patient's well control of hemoglbulin, calcium, albumin and long duration on hemodialysis.

Conclusion Patients on maintenance dialysis typically show a suboptimal immune response to hepatitis B virus vaccine compared with the non-uraemic population.

Keyword Hemodialysis, chronic renal failure, HBsAg, vaccination.

List of abbreviation: Anti HCV = anti-hepatitis C virus, DM = diabetes mellitus, CRF = chronic renal failure, CKD = chronic kidney disease, ESRD = end stage renal disease, HD = hemodialysis, HBV = hepatitis B virus, HLA = human leukocyte antigen, RRT = renal replacement therapy, rHuEPO = recombinant human erythropoietin, Hb = hemoglobin.

Introduction

In haemodialysis (HD) patients, hepatitis B virus (HBV) infection has higher mortality and morbidity rate is more likely to result incarrier state. Although Hepatitis B vaccine is effective in producing protection against HBV infection, the antibody response may be variable [1].

Blood is a major vehicle for the transmission of the HBV. Therefore, patients undergoing regular HD are at particularly high risk of exposure to HBV infection, with a wide variation in endemicity between the countries. In addition, immunodeficiency renders patients with end stage renal disease (ESRD) susceptible to infection and subsequent disease [2].

Uremia impairs not only the clearance of the virus but also antigen presentation, T-cell activation, and subsequent antibody production. HBV vaccination is recommended for all predialysis and dialysis patients, but the seroconversion rate of anti-hepatitis B surface

antigen (anti-HBs >10 IU/l) and adequate responses (anti-HBs >100 IU/l) are markedly lower, quite variable, and shorter lasting than inhealthy immunocompetent subjects. Therefore, patients with chronic kidney disease (CKD) should undergo vaccination in the early stages of the disease when the primary immune response is still intact [3].

Despite the use of HBV vaccines and preventive measures, infection with HBV remains a major global health problem. Patients with CKD are at an increased risk of acquiring HBV infections from shared dialysis equipment, increased exposure to blood products, and immune-deficiency associated with CKD In addition, they may be more likely to develop chronic infections on exposure to HBV [4,5].

HBV infection remains a concern in dialysis populations, because the vaccination programs have been less successful in these populations than in the general population. The causes of poor seroconversion in CKD patients include malnutrition, uremia, and immunosuppression due to renal failure [6].

Various approaches have been adopted to improve the response rate to hepatitis B vaccine in ESRD including the increased vaccine dose [7], additional vaccine inoculations and the use of intradermal route rather than intramuscular vaccine route [8].

Ineffective vaccination is predictive for prevalence and incidence of HBsAg positivity and anti- hepatitis C (anti-HBc) positivity [9]. At present, the attention of nephrologists is focused on CKD patients, who are currently non-dialyzed, but as their kidney disease progresses, it is likely to lead to renal replacement therapy (RRT) in the future. Hepatitis B vaccination of such patients is thought to decrease a number of HBV susceptible patients on RRT [10].

Moreover, an anti-HBs titer tends to fall with time in persons who mounted an antibody response. In dialysis patients, the loss of hepatitis B immunity seems to be quicker than in healthy subjects [11].

Numerous inherited and/or acquired factors are implicated in diminished immunization following hepatitis B vaccination. However, at first, in this study should exclude variables such as improper storage or administration that is not compatible with a manufacturer instruction. Involvement of genetic factors in the anti-HBs development is continuously examined. Already in the seventies of the past century, immune response to HBsAg in HBV infected HD patients was linked to human leukocyte antigens (HLA) [12].

Immune response to HBsAg in HBV infected HD patients was linked to HLA, possession of major histocompatibility complex haplotype HLA-B8, SCOI, DR3, interleukin genotypes (i.e., IL-10, IL-12, IL-18) were associated with the anti-HBs development in response to HBsAg in HD patients [13].

Methods

Prospective study involved one hundred patients (56 male and 44 female) of different age groups range from 22-75 years. Their mean age was 47±21years were complaining of chronic renal failure (CRF) on regular HD in Al-Imamain Al-Kadhimain Medical City for the period from June 2014 to July 2015.

Demographic and clinical variables including age, gender, cardiovascular disease, cancer, infection, HD vintage, use of fistula or central vascular access were analyzed. Therapeutic and laboratory variables, erythropoietin dose, the levels of blood urea, creatinine, serum calcium, total protein, serum albumin, hemoglobin (Hb) level, Kt/V (adequacy of dialysis) and anti-HBS titer were monthly analyzed.

Screening for HBsAg and total antibody to HBsAg and Anti-HCV were performed by ELISA method. Patients negative for HBsAg and anti-HBs were vaccinated with 40µg of Euvax B (LG Life Sciences, Korea) intramuscularly in the deltoid muscle by following a schedule of 0, 1, 2 months. Seroconversion was defined as an antibody titer equal to or more than 10IU/mL. The antibody titer was tested at third month and if the titer was <10 (non-responded) or 10-

100IU/mL (partial responded) respectively they were given another fourth dose (40µg) of vaccine at sixth month.

Statistical analysis was performed using chi-square test. At level of significance $p \leq 0.05$ regarded as statistical significant.

Result

The etiology of ESRD was DM in 37%, hypertension in 30%, obstructive uropathy in 7%, glomerular disease in 4%, autosomal dominant polycystic kidney disease in 4%, vasculitis in 3%, and interstitial nephritis in 3% and unknown causes in 12% (Table 1).

Table 1. Primary renal diseases causing end stage renal disease and the response to HB vaccine related to number of doses.

Causes of chronic renal failure	Number	Response to hepatitis B vaccine						p value
		1st dose	2nd dose	3rd dose	4th dose	≥4 doses	Total	
Diabetes mellitus	37	4	3	5	6	4	22	0.0221
Hypertension	30	3	6	4	3	2	18	1.745
Obstructive uropathy	7	-	2	1	-	1	4	4.757
Glomerular disease	4	1	1	1	-	1	3	6.016
ADPK	4	1	2	-	-	-	3	6.016
Vasculitis	3	-	-	-	1	1	2	1.370
Interstitial nephritis	3	-	-	2	-	-	2	1.0259
unknown	12	1	4	2	-	2	9	5.4228
Total	100	9%	18%	15%	10%	11%	63%	

ADPK=autosomal dominant polycystic kidney disease

Responded to 1st dose vaccination 9% of patients with end stage renal disease, 18% responded to the second dose, 15% responded to the third dose, 10% responded to fourth dose of vaccination and 11% response to vaccination for more than four doses of vaccination.

In the current study, thirty one percent (31%) of patients were anti- HCV positive; 18 (58%) were responding to hepatitis B vaccination and 13 (42%) not response to Hepatitis B vaccination. There were variations in response to hepatitis B vaccine in relation to other parameter; age, sex, HCV status and DM, have no effect on response to hepatitis B vaccine ($p = 0.1072, 0.1711, 0.4932, 0.2388$, respectively) while the Hb level, serum calcium, serum albumin and duration of dialysis showed significant effect on the response to hepatitis B vaccine in ESRD ($p = 0.0323, 0.0076, 0.0002, 0.0013$, respectively) as mention in table 2.

Discussion

With the introduction of hepatitis B vaccine in the 1980, it was hoped that HBV would be eliminated from dialysis population. Although HBV has not been eradicated yet, the vaccine has helped to reduce the incidence further, but with suboptimal efficacy in patient with CRF. Currently available hepatitis B vaccines have an excellent safety and immunogenicity profile, conferring seroprotection in more than 95% of the vaccinated population [(14)]. The rate of seroconversion to hepatitis B vaccine among individuals with CRF on HD in current study is 63%, near to other study by Hashim et al [(15)] in Iran who was found 78%. Bel'eed et al [(16)] also found that seroconversion rates were similar in HD patients (66%; 90/136). In another local study in Iraq, it was found that 77.7% of vaccinated subjects were apparently healthy after receiving the full course of vaccination and had protective titer of anti-HBS [(17)].

Table 2. Hepatitis B vaccine responses to clinical and laboratory parameters

Characteristic		Response to vaccination		p value
		Yes	No	
Gender	Male	32	24	0.171
	Female	31	13	
Age (years)	> 40	44	20	0.107
	< 40	19	17	
Hepatitis C virus	Positive	18	13	0.493
	Negative	45	24	
Serum calcium	≥ 8.5 mg	22	20	0.007
	≤ 8.5 mg	50	17	
Serum albumin	≥3.5 mg	55	20	0.000
	≤ 3.5 mg	8	17	
Hemoglobin level	≥ 10 g/dL	15	22	0.032
	≤ 10 g/dL	13	15	
Duration of dialysis (months)	≥ 6	46	15	0.001
	< 6	17	22	
Diabetes mellitus		22	17	0.238

Lower responsiveness to hepatitis B vaccination occurs despite recommendations to use higher vaccine doses (40µg) in HD patients than in general population. There are many explanation for this may be duo to immuncompromised patients, delaying vaccination until ESRD, genetic factor, poor complain with dialysis, route of administration of the vaccine by intramuscular rather than intradermal and generation of vaccine.

Elderly and male patients show similar response to the young age and female patients (p = 0.171 not significant) in contradiction to the study of McNulty [18] who noticed lower rate of seroconversion in elderly and male patients.

In the current study, patients with HCV-infection did not show a significant decrease in their response rates among HCV-infected versus non-infected patients (p = 0.493). Most of the patients who responded to vaccination of hepatitis B vaccine have controlled Hb (above 10g/dL) in comparison to others who not responsed to vaccination (p = 0.032) duo to the treatment with rHuEPO that increases antibody titers after hepatitis B vaccination in dialysis patients. There is much evidence suggesting that rHuEPO may influence the immune response because of its effects on the cells of the humeral and cellular immune system [19].

The patients who responded to vaccination have well controlled calcium level (p = 0.007). This is supported by other study that showed vitamin D deficiency is associated with poor response to active hepatitis B immunization in patients with CKD [20].

Normal serum albumin was found to enhance the response to hepatitis B vaccine in HD patients (p = 0.0002) duo to good nutritional state. This sis also noticed by Fabrizi [6].

Long duration of HD showed good responses to hepatitis B vaccine (p = 0.001) because patients are receiving more doses of vaccination (more than five doses), good nutritional state and control on other parameter such as albumin, calcium and hemoglobin.

In conclusion, viral hepatitis continues to be a relevant topic for HD centers, although the number of infected dialysis patients is declining in most countries. Immune response to hepatitis B vaccine affected by well control of Hb, calcium, albumin and long duration on HD.

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Conflict of Interest

The author declare no conflict of interest

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