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Renal Data from Asia–Africa

Immune Response to Hepatitis B Vaccine in Health-Care Workers

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ABSTRACT. This study was performed to study the immune response to hepatitis B virus (HBV) vaccine in health-care workers. Through a cross-sectional study, relevant information and blood samples from 151 healthcare workers at the Firuzgar hospital were studied. The age range of the study individuals was 20–59 years, with the mean and standard deviation being 35.11 and 10.06, respectively. There were 24 males (15.9%) and 127 females (84.1%). The mean and median of months after HBV vaccination was 63.42 and 49.00, respectively. The mean and median of anti-HBs titer in those who received HBV vaccination was 164.81 and 200 milli international units per milliliter (mIU/mL), respectively. Of the 129 HBV-vaccinated subjects, 103 (68.2%) had anti-HBs titer >10 and 26 (17.2%) had anti-HBs titer <10. There was no association between gender and anti-HBs titer, but vaccination and adequate completion of its courses were associated with higher anti-HBs titer ($P < 0.05$). Also, the logistic regression method showed that the association between duration after vaccination and age with anti-HBs titer was not statistically significant. Our study suggests that the HBV vaccine immunization program had obtained excellent efficacy. There is need for further investigation among subjects who are not vaccinated against HBV but are positive for anti-HBs as well as in HBV-vaccinated subjects with low anti-HBs titers, about possible low-level viremia and other causes of lower vaccine efficacy, particularly in health-care workers.

Introduction

In a study, a model was developed to calculate the age-specific risk of acquiring hepatitis B virus (HBV) infection, acute hepatitis B (illness and death) and progression to chronic HBV infection. The effect of hepatitis B vaccination was calculated from vaccine efficacy and vaccination series coverage, with and without the administration of the first dose of vaccine within 24 hours of birth (i.e., birth dose) to prevent perinatal HBV infection. For the year 2000, the model estimated that 620,000 persons died worldwide from HBV-related causes:

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580,000 (94%) from chronic infection-related cirrhosis and hapatocellular carcinoma and 40,000 (6%) from acute hepatitis B. In the surviving birth cohort for the year 2000, the model estimated that, without vaccination, 64.8 million would become HBV infected and 1.4 million would die from HBV-related disease. Routine infant HBV vaccination, with 90% coverage and the first dose administered at birth, would prevent 84% of the global HBV-related deaths.[1]

A mass campaign of immunization against hepatitis B was undertaken for those born from 1989 to March 2007 in Iran. During this campaign, 1,320,000 people were vaccinated and about 90% coverage was reached. Hepatitis B vaccination takes years if not decades to show effectiveness in the community. In 2002, considering the country's health needs and priorities, the program also recommended vaccinating people with high-risk occupations like firefighters, workers of city hall, etc. It was concluded that 12% of the first target group was already vaccinated against HBV. The health infrastructure to expand the coverage for more vaccination is accessible in Iran, and this approach will decrease the incidence rate in the Iranian population, especially if followed by these considerations: educating the people, especially the at-risk group; implementing strategies to prevent transmission to others and screening and finding the patients in early stages and asymptomatic phase.[2]

Although protective anti-HBs response rates after HBV vaccination typically exceed 90%, a number of factors can impede an adequate antibody response. Smoking, obesity, injection into the buttock, chronic liver disease, presence of human leukocyte antigens (HLA)-DR3, DR7 and DQ2 alleles, absence of the HLA-A2 allele and extremes of age may be associated with reduced immunogenicity. The response rates are also lower in immunocompromised patients, such as transplant recipients, patients receiving chemotherapy and those with end-stage liver disease. Patients with chronic kidney disease should be vaccinated early in the course of their disease, before the renal disease progresses, to ensure optimal response to vaccination.[3]

In Iran, Cuban hepatitis B vaccine became available approximately in 1994 and mass vaccination of neonates and children was incorporated in the national vaccination scheme.[4] Healthcare workers (HCWs) are at a high risk of acquiring HBV. The seroconversion rate after HBV vaccination in Pakistani HCWs was similar to that reported in the western and neighboring populations. HCWs with a reduced immune response to HBV vaccine in a high-disease-prevalent population are at greater risk. Therefore, it is crucial to check post-vaccination HBsAb in all the HCWs. This strategy will ensure safety at work by reducing nosocomial transmission and will have a cost-effective impact at an individual as well as a national level, which is very much desired in a resource-limited country.[5]

In this manuscript, the immune response to HBV vaccine in HCWs at the Firuzgar Hospital, who had been immunized by HBV vaccine, is studied.

Methods

The immune response to HBV vaccine in 151 hospital employees of the Firuzgar Hospital was investigated. They were questioned as to whether they had received HBV vaccine before or not and, if vaccinated, were asked whether they had completed three courses of the vaccine. All individuals who had not received HBV vaccine earlier or those vaccinated with anti-HBs titer equal to or less than 10 mIU/mL were assessed. One hundred and forty (92.7%) of them were medical personnel, including nurses and laboratory technicians, and 11 (7.3%) were hospital-cleaning staff. Distribution of anti-HBs antibodies and its correlations was studied. Participants signed the consent form and the proposal was approved by the local ethics committee of the hospital.

Statistical Analysis

Statistical analyses were performed using SPSS statistical software (version 16.0, 2007; SPSS). Frequencies were obtained by direct counting. Data of samples were analyzed by a chi square

Table 1. Distribution and correlation of anti-HBs titer with the variables.

Variables	Anti-HBs titer <10 mIU/mL	Anti-HBs titer >10 mIU/mL	Total	X^2	*P*-value
Male	9 (6%)	15 (9.9%)	24 (15.9%)		
Female	26 (17.2%)	101 (66.9%)	127 (84.1%)		
Total	35 (23.2%)	116 (76.8%)	151 (100%)	3.287	0.070
Medical healthcare workers	31 (20.5%)	109 (72.2%)	140 (92.7%)		
Cleaning staff	4 (2.7%)	7 (4.6%)	11 (7.3%)		
Total	35 (23.2%)	116 (76.8%)	151 (100%)	1.158	0.282

goodness of fit test and logistic regression method. The correlations were compared by chi square test and logistic regression method, respectively. The odds ratio (OR) and 95% confidence interval (CI) for the occurrence were computed. All two-tailed *P*-values of <0.05 were considered to be statistically significant.

Results

The age range of the study individuals was 20–59 years, and the mean and standard deviation were 35.11 and 10.06, respectively. There were 24 males (15.9%) and 127 females (84.1%). At the time of sampling, 129 subjects (85.4%) had received HBV vaccine earlier and 22 (14.6%) had not. Among the vaccinated subjects, according to the subjects' statement, 113 had completed the three courses of HBV vaccination and 16 cases had not. Of the 151 subjects studied, 35 (23.2%) had anti-HBs titer <10 and 116 (76.8%) had anti-HBs titer more than 10 mIU/mL. Of the 129 HBV-vaccinated subjects, 103 (68.2%) had HBsAb titer >10 and 26 (17.2%) had HBsAb titer <10 mLU/mL. The difference between anti-HBs titer in those vaccinated (129, 85.4%) and those not vaccinated (22, 14.6%) was significant (X^2: 4.546, *P*-value: 0.033). The difference between anti-HBs titer in the medical personnel and the cleaning staff was not significant (X^2: 1.158, *P*-value: 0.282).

Our results show that variables of gender and medical health workers *versus* cleaning staff in the hospital were not associated with anti-HBs titers ($P > 0.05$). However, variables of vaccination and completeness of its course were positively associated with anti-HBs titer ($P < 0.05$) (Table 1). Also, the logistic regression method shows that association between length of time after vaccination and age with anti-HBs titer was not statistically significant (Table 2).

The mean and median of months after HBV vaccination were 63.42 and 49.00, respectively. The mean and median of anti-HBs titer in those who received HBV vaccination were 164.81 and 200, respectively. Among the HBV-vaccinated subjects (129), the difference in anti-HBs titer between those who completed *versus* those who did not complete the course of vaccination, by independent samples T-test, was not significant (Table 3).

Discussion

The results of our study suggest that it is necessary to investigate the possible low-level viremia and other causes of lower immune response to HBV vaccine in HCWs. Hepatitis B vaccines are highly effective and safe and have been incorporated into national immunization programs in over 150 countries. The major humoral immune response is to the common determinant of the surface antigen protein of the virus.[6] In a study of 538 children who had received three doses of Cuban hepatitis B vac-

Table 2. Correlations and prediction of anti-HBs titer with age and date of vaccination by logistic regression.

Variables		B	SE	Wald	Df	Sig.	Exp (B)	95.0% CI for EXP (B)	
								Lower	Upper
Step 1	Date of month	0.132	0.226	0.342	1	0.558	1.141	0.733	1.776
	Group of age	0.077	0.085	0.838	1	0.360	1.081	0.915	1.276

Table 3. Statistical difference between anti-HBs titer in those who completed *versus* those who did not complete the course of vaccination.

Completed course		***N***	**Mean**	**Std. deviation**	**t**	**df**	**Sig. (two-tailed)**
Anti-HBs titer	Yes	113	168.49	124.796	1.131	147	0.260
	No	16	140.89	135.851			

cine, 305 (56.7%) were good responders, 149 (27.7%) were hyporesponders and 84 (15.6%) were non-responders. In this study, the concentration of anti-HBs in good responders was low and the rate of hyporesponders and non-responders was high. This suggests that anti-HBs titer should be measured in all Iranian vaccinees after the third dose of vaccination with the Cuban HBV vaccine, such that the health authorities can decide which scheme of vaccination is to be implemented.[4]

Lack of adequate HBsAb formation may be due to the persistent exposure of HCWs to HBV infection and low-level viremia or, also, infection with mutant forms from patients on certain anti-viral treatments. In a study, 94 negative HBsAg, negative anti-HBs and positive anti-HBc cases and 56 persons with negative HBsAg, anti-HBs and anti-HBc controls were vaccinated with recombinant hepatitis B vaccine. A higher percent of married cases together with a higher percent of positive HBsAg in spouses may explain the slight difference in the response to vaccination in the case group in comparison with the control group as a result of a booster-like effect, which seldom happens because of recurrent contacts between the subjects and the HBsAg-positive spouses.[7]

An interventional, descriptive study conducted on children who had been immunized with Cuban recombinant hepatitis B vaccine reported that their antibody titers were <10 mIU/mL (non-responder), while these was 10–100 mIU/mL (hyporesponder) in those who received a booster dose of the same vaccine in their deltoid muscles. The response of these 141 children, whose mean age was 1.9 years, to the booster dose of vaccine was 94.3% and 100% with the first and second booster dose of the vaccination, respectively. The study demonstrated moderately increased antibody production in the majority of vaccines with single supplementary vaccine.[8]

Among 600 HCWs interviewed in a referral hospital in Shiraz, Iran, 339 subjects were vaccinated with three doses of HBV vaccine. The anti-HBsAb titers were >100 mIU/mL in 211 subjects (62.2%), 10-100 mIU/mL in 85 (25.1%) and <10 mIU/mL in 43 (12.7%) persons. Among these subjects, 273 were vaccinated when they were <5 years old, 47 cases were vaccinated when they were between 5 and 10 years of age and 19 cases were vaccinated when they were aged more than 10 years. The majority of the study subjects had an antibody concentration above the protective level. Re-assessment for vaccination should be considered in HCWs according to their anti-HBsAb levels 10 years after vaccination.[9]

Vaccination of healthy adults with recombinant hepatitis B (rHB) vaccine fails to induce a protective antibody response in a proportion of individuals. Imbalanced T-helper 1 (Th1)/Th2 response has been attributed to the lack of specific antibody response to rHB vaccine. In a study, *in vitro* production of interleukin-2 (IL-2), interferon (IFN)-gamma and IL-10 was investigated in Iranian healthy adults vaccinated with the rHB vaccine. Peripheral blood mononuclear cells (PBMC) were isolated from 18 high-responders and eight non-responders and stimulated with rHB antigen or phytohemaglutinin (PHA) mitogen. The results demonstrated a significant decrease in the production of IL-2, IFN-gamma and IL-10 ($P < 0.005$) in response to the rHB antigen. The levels of all cytokines induced by PHA were similarly represented in both groups of vaccinees. These findings suggest that unresponsiveness to rHB vaccine may be caused by inadequate Th1- and Th2-like cytokine production.[10]

The persistence of anti-HBs depends on the peak antibody level achieved after three doses.[11-14] Unresponsiveness to HB vaccine has been attributed to a number of environmental and genetic factors, the most important ones

being the haplotype of HLA antigens and immunological tolerance.[15] A variety of HLA class I and II antigens have been reported to be associated with unresponsiveness to the vaccine in different ethnic populations.[16]

Different responses of clonal selection to the immunizing antigen in different human populations mean that any definition of anamnestic response must recognize the role of ethnicity.

There remain problems with interpreting the long-term protection against HBV infection. Follow-up studies are needed for surveillance of break-through infections. Also, sub-clinical infections (formation of anti-HBc in the absence of HBsAg) need to be distinguished from actual breakthrough infections (presence of HBs Ag and clinical disease). Furthermore, in countries where the endemicity of hepatitis B is low, clinically significant breakthrough infections (as a marker of waning immunity) will be rare. For studies in developing or highly endemic countries, further complications for interpretation include maternal hepatitis B status, dose and route of immunization of infant, the frequent lack of documentation of post-immunization response, other infections (in particular, HIV infection) and nutritional status.[17]

In conclusion, the HBV vaccine immunization program had obtained excellent efficacy and immune response in HCWs. Causes of vaccine failure and HBV variants need to be assessed in this group. This study showed the need for further immunologic and molecular investtigation in subjects with no HBV vaccination but positive anti-HBs and also in HBV-vaccinated subjects with a low level of anti-HBs titer about the possible low-level viremia and causes of lower efficacy, respectively, in HCWs.

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