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Original Article

Microbiology Section

Estimation of Anti-Hepatitis B Antibody Status of Vaccinated Health Care Workers in a Medical College Hospital in Central Kerala, India

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ABSTRACT

Introduction: Healthcare professionals in developing countries have high risk for acquiring Hepatitis B Virus (HBV) infection. Vaccination of this risk group is the only remedy to reduce occupational HBV infection. Hepatitis B surface antibody (anti-HBs) titer is a reliable marker for protective immune response in the vaccinees. Non-responders continue to be at risk of acquiring HBV infection. Most of the Health Care Workers (HCWs) in the institution where the study was conducted has taken full course of HBV vaccination within past two years. Estimation of their immune status following vaccination can help them to decide about the post-exposure prophylaxis during occupational exposure.

Aim: To estimate the anti-HBs titer of HCWs who has been fully vaccinated with Hepatitis B vaccine and to observe the pattern of anti-HBs titer with age, sex, Body Mass Index (BMI) and diabetic status of the participant.

Materials and Methods: A descriptive study was conducted on 50 vaccinated HCWs. Their anti-HBs titres were estimated using Enzyme Linked Fluorescent Assay (ELFA) technique and were classified in to non-responders, weak responders and good responders. The pattern of anti-HBs titer with age, sex, BMI and diabetic status of the participant was also observed. Statistical analysis was done using SPSS 21. The p-value <0.05 was considered as statistically significant.

Results: Among the study population, 96% showed seroconversion in response to the Hepatitis B vaccine. Among them 86% were good responders and 10% weak responders. No statistically significant association was found between mean age, sex, BMI and diabetic status with immune response (p>0.05).

Conclusion: Majority of the study population achieved adequate anti-HBs antibody levels after a full course of vaccination. The non-responders in the study population point towards the need for the estimation of post-vaccination antibody titer as they may be comparatively vulnerable to HBV infection. Mandatory HBV vaccination and post-vaccination anti-HBs titer estimation in HCWs should be emphasised to make dramatic reduction in the incidence of the disease following an occupational exposure.

Keywords: Antibody response, Hepatitis B vaccine, Occupational exposure

INTRODUCTION

Hepatitis B is a highly infectious disease. According to World Health Organisation (WHO), the global prevalence of HBV infection in the general population was estimated as 3.5% with about 257 million persons living with chronic HBV infection [1]. The infection includes a wide spectrum of diseases, ranging from hyper acute fulminant hepatitis to refractory cirrhosis and hepatocellular carcinoma [2]. Infection can result in chronic carriage of the virus and around 300-400 million carriers are estimated worldwide [3]. The carriers can act as reservoirs of the virus and later may go on for chronic liver diseases.

Healthcare professionals in developing countries have the highest risk of HBV infection. It is estimated that sharps injuries account for 40-60% of occupational HBV infection in developing countries [4]. In an unvaccinated individual, the risk of acquisition of HBV infection after single exposure of HBV infected blood or body fluid ranges from 6%-30% [5]. Among healthcare professionals seroprevalence is 2-4 times higher due to exposure to blood and other infected body fluids [6,7]. Fortunately, there is vaccination against this virus which is 95% effective. Vaccination of the risk group is the only remedy to reduce occupational HBV transmission. Vaccination schedule currently followed is of three doses at 0-1-6 months intramuscularly [2,3].

Hepatitis vaccine confers long term protection. Hepatitis B surface antibody (anti-HBs) titer is a reliable marker for protective immune response. According to Centre for Disease Control (CDC), anti-HBs levels decline rapidly within the first year and thereafter, more slowly in second year. However, there will be persistence of protective antibody titer up to 5-10 years of primary vaccination [8-10]. Antibody titer of 10 IU/L after three doses of vaccine is considered protective [7,8]. An antibody titer >100 IU/L will be shown by most of the people within 6-8 weeks of completed vaccination. However, some individuals do not show a protective anti-HBs antibody response even after a complete course of primary vaccination [9,10]. It is estimated that 5-15% of people who are vaccinated come under this group and continue to be at risk of acquiring hepatitis B [10]. According to numerous studies, variation in antibody titer in each individual depends on their age of vaccination, sex, smoking and exposure to the individual with HBV infection [11,12]. WHO recommends mandatory HBV vaccination for all the HCWs as they form essential part of the risk group [13]. Most of the HCWs in the institution have taken full course of HBV vaccination within past two years.

Hence, the aim of present study was to determine the anti-HBs titer in HCWs of the institution who have been certified as completely immunised with three doses of HBV vaccines and to observe the pattern of their anti-HBs titer with age sex, BMI and diabetic status. Estimation of the post-vaccination anti-HBs titer will help them to know about their immune status against HBV infection and to plan about the post-exposure prophylaxis during any occupational exposure.

MATERIALS AND METHODS

A descriptive study was conducted among the vaccinated HCWs who have taken 0-1-6 doses of HBV vaccination in Sree Narayana Institute of Medical Sciences, Ernakulam, Kerala, India. The study was done during the months of May and June of 2018. Approval from Institutional Research Board (IRB) and Institutional Ethics Committee (IEC/12/01) were obtained before the commencement of the study.

The total number of vaccinated HCWs in the year 2016 was obtained from the vaccination register maintained in the hospital. All were vaccinated in a mass vaccination campaign conducted in the institution with same brand of recombinant Hepatitis B vaccine. They have not taken any booster doses. Informed consent was obtained from all the HCWS who got vaccinated in the year 2016. Fifty participants who received vaccine, gave the consent were selected by simple random sampling method. A self-administered questionnaire prepared by the investigators in consultation with the IRB and the statistician was given to the 50 participants. It included questions on demographics, including name, age, sex and job category; past history of confirmed HBV infection; medications for diabetes mellitus and smoking habits. The data from the questionnaire was analysed and their vaccination status was confirmed. The BMI was calculated from the data using the formula BMI=weight (kg)/height^2 (m^2). All data were stored anonymously and handled only by the investigators.

Five ml of blood was collected from them after obtaining informed written consent, under all aseptic precautions. The serum was separated and transported to a nearby accredited Lab for anti-HBs titer estimation. The titer was estimated using the VIDAS Anti-HBs Total II Kit. It is an automated quantitative test for the immunoenzymatic detection of antibodies to Hepatitis B Surface Antigen (HBsAg) in human serum using the ELFA technique [14]. Results were calculated automatically by the instrument in relation to the calibration curve stored in its memory and then print was taken. The values were obtained in mIU/ml and expressed in IU/L [14]. The participants were categorised into 3 groups on the basis of their antibody titer in the serum [15].

Non-responders: Serum level <10 IU/L.

Weak responders: Serum level between 11-100 IU/L.

Good responders: Serum level >100 IU/L.

STATISTICAL ANALYSIS

The data was entered in MS-EXCEL and statistical analysis was done using SPSS 21. Frequency and percentage was calculated. ANOVA test was used for finding the significant difference of the mean values and Chi-square test was used for finding the association between the variables. The p-value <0.05 was considered as statistically significant

RESULTS

Out of the 50 participants, 13 (26%) were nurses, 17 (34%) lab technicians, 13 (26%) housekeeping staff and 7 (14%) paramedical students. This included 48 (96%) females and 2 (4%) males. Mean age of the participants was 37±11.502 years. None of them were smokers.

Sixteen (32%) of the HCWs belonged to the age group 20-29 and 8 (16%) belonged to age group 50-59 [Table/Fig-1]. Forty-eight (96%) of the HCWs showed protective titers, of which 5 (10%) were weak responders and 43 (86%) were good responders. Two (4%) showed lack of protection. Ninety four percent of lab technicians and 100% of paramedical students showed good immune response while 15.4% of the nurses had non-protective titers [Table/Fig-2]. Age group of 20-29 years showed higher rate of good immune response which is 93.8%. Non-responders remained distributed equally between the age group 30-39 and 40-49 years. Two (4%) of the HCWs were underweight, 33 (66%) normal weight and 15 (30%) overweight. Good immune response was shown by 87.9% of normal weight HCWs. One each of the normal and overweight HCWs was non-responder [Table/Fig-3]. No statistically significant association was found between seroconversion rate and sex, mean age and BMI with p>0.05 [Table/Fig-4,5]. Hundred percent of the diabetics and 95.8% of non-diabetics were seropositive. All the diabetic patients were females. No statistically significant association was found between diabetic status and immune response (p>0.05) [Table/Fig-6].

Age (years)	No. of participants (%)
20-29	16 (32%)
30-39	12 (24%)
40-49	14 (28%)
50-59	8 (16%)
Total	50 (100%)

[Table/Fig-1]: Distribution of participants according to age.

Anti-HBs response	Profession (%)				Total
	Nurses	Lab technician	House keeping staff	Student	
Non-responders (<10 IU/L)	2 (15.4)	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Weak responders (11-100 IU/L)	3 (23.1%)	1 (5.9%)	1 (7.7%)	0 (0%)	5 (10%)
Good responders (>100 IU/L)	8 (61.5%)	16 (94.1%)	12 (92.3%)	7 (100%)	43 (86%)
Total HCWs	13	17	13	7	50

[Table/Fig-2]: Distribution of participants according to immune response.

Immune response groups	Age groups				BMI		
	20-29 years	30-39 years	40-49 years	50-59 years	Underweight (<18.5)	Normal (18.5-24.9)	Overweight (25-29.9)
Non-responders	0 (0%)	1 (8.3%)	1 (7.1%)	0 (0%)	0 (0%)	1 (3%)	1 (6.7%)
Weak responders	1 (6.2%)	1 (8.3%)	2 (14.3%)	1 (12.5%)	0 (0%)	3 (9.1%)	2 (13.3%)
Good responders	15 (93.8%)	10 (83.4%)	11 (78.6%)	7 (87.5)	2 (100%)	29 (87.9%)	12 (80%)
Total	16	12	14	8	2	33	15

[Table/Fig-3]: Distribution of immune response of participants according to age and BMI.

Sex	Seroconversion		Total
	Positive	Negative	
Male	2 (100%)	0 (0%)	2
Female	46 (95.8%)	2 (4.2%)	48

[Table/Fig-4]: Distribution of participants according to gender and seroconversion.
p-value=0.921; χ^2=0.087 degree of freedom (df)=1

Immune response group	Mean Age±SD	F-value	p-value	Mean BMI±SD	F-value	p-value
Good responders	36.28±11.79	0.615	0.545	22.8±3.29	1.923	0.158
Weak responders	42±10.89			25.2±2.26		
Non-esponders	40±2.82			25.9±3.89		

[Table/Fig-5]: Comparison of mean ages and BMI of different immune response groups.
F-value determined by anova test

Diabetic status	Seroconversion		Total
	Positive	Negative	
Diabetic	2 (100%)	0 (0%)	2
Non-diabetic	46 (95.8%)	2 (4.2%)	48

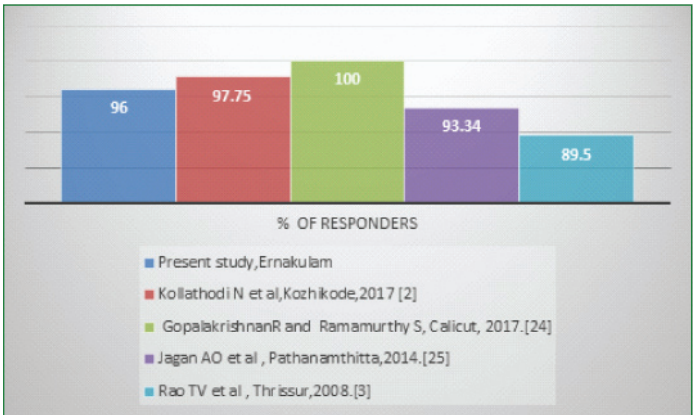
[Table/Fig-6]: Comparison of immune response according to diabetic status.
p-value=0.921; χ^2=0.087 df=1

DISCUSSION

Among the 50 HCWs included in the present study, 96% showed seroconversion in response to the hepatitis B vaccine. Among them, 86% were good responders and 10% weak responders. The prevalence of immune responders following a primary HBV vaccination from different parts of india and kerala is given in [Table/Fig-7,8], respectively [2,3,16-25]. The data projects the immune response which was estimated within a period less than five years of post-primary vaccination.

Studies from India	% of responders	% of non-responders
Present study, Ernakulam, Kerala	96%	4%
Sharma T et al., Dehradun, 2019 [16]	90.3%	9.7
Prashant P et al., Noida, 2018 [17]	84.5	15.5
Basireddy P et al., Andra Pradesh, 2018 [18]	96.5	3.5
Sahana HV et al., Karnataka, 2017 [19]	94.1	5.9
Lakshmi J et al., Hyderabad, 2017 [20]	93.55	6.45
Lakshmanan KP et al., Tripura, 2017 [21]	96%	4%
Batra V et al., Rajasthan, 2015 [22]	70	30
Mahawal BS et al., New Delhi, 2013 [23]	99.9	0.1

[Table/Fig-7]: Prevalence studies from different states of India [16-23].



[Table/Fig-8]: Prevalence studies from different parts of Kerala [2,3,24,25].

In a study conducted by Hussein MM and Hussein MM, the seroconversion rate was 96%, of which 92% were good responders and 4% were weak responders [15]. In a contemporary study by Mohsenzade M et al., 87.8% of the subjects were good responders while 8.9% were weak responders [26]. In a similar study conducted by Mahawal BS et al., 80% were good responders while 19.9% showed weak response [23]. These results indicate that HBV vaccine is highly effective and it should be administered to all individuals at risk, especially HCWs. But some studies showed a lower response rate of 80.1% and 70% [22,27].

In the present study, 4% of the subjects were non-responders. Several studies reports that the non-responders range between 5-15% [10]. Surprisingly, studies from Rajasthan and Bulgaria showed a higher non-response rate of 30% and 20%, respectively [22,27]. There are diverse opinions regarding the management strategy for initial non-responders. According to some authors, the "initial non-responders" should be given a second series of HBV vaccination after ruling out hepatitis B infection [24,25]. About 30-50% of them show seroconversion after second series of vaccination [4,28]. In a study from Southern India, a single booster dose seroconverted 100% of the initial non-responders [2]. But, some authors suggest a fourth dose and retesting after two months. If no response is elicited again, only then a full course of the conventional vaccine at standard doses is administered and retested after 1-2 months from the last dose [28]. Some authors recommend boosters in immunocompromised HCWs only [4]. Considering these facts, non-responders to primary series of vaccination who are HBsAg negative should be regarded as susceptible to HBV infection and should be counselled about the infection control measures to be taken to prevent HBV infection. They should also be motivated to obtain Hepatitis B Immunoglobulin (HBIG) prophylaxis for any known or probable parenteral exposure to HBsAg positive blood.

The weak responders accounted for 10% of the population in the study. Some authors recommend booster doses in such individuals because of insufficient proof of long term protection [27]. However, most authors do not recommend periodic evaluation or booster doses for initial "weak responders" as continued vaccine induced protection is presumed to occur as a result of immune response preservation by selective expansion and differentiation of clones of antigen specific B and T lymphocytes [27,28].

Many authors propose older age of primary vaccination, female gender, obesity, smoking habits and diabetes as factors which decrease the response rate to HBV vaccination [25,26,29]. Hence, the study analysed the age, sex, BMI, diabetic status and smoking habits in the study population in relation to the pattern of response to HBV vaccine.

In the present study, age was not a significant determinant of response to HBV vaccine similar to study conducted by Zamani F et al., [30]. But, reports by Kollathodi N et al., Chaudhari CN et al., Zeeshan M et al., Hussein MM and Hussein MM, Louther J et al., and Yen YH et al., demonstrated a significantly lower mean age for good responders when compared to weak responders and non-responders [2,4,5,15,31,32]. No significant association between sex and anti-HBs levels was observed in the present study. This is consistent with the reports by Kollathodi N et al., Chaudhari CN et al., and Baghianimoghadam MH et al., where they found out that anti-HBs production was not affected by sexual factors such as feminine hormones [2,4,33]. In this study, BMI was also not significantly different among different responders groups as reported by other workers [4,25,34]. These could be attributed to small sample size. None of the study subjects were smokers. Cigarette smoking is associated with series of alterations in immune function. It has been supposed that the diminished response in smokers maybe due to the increase in T suppressor lymphocytes [35].

There was no significant difference in the response rate of diabetics and non-diabetics in the study. Schillie SF et al., and Elrashidy H et al., found that the diabetic individuals display significantly decreased levels of anti-HBs titer after vaccination [36,37]. These inconsistent results may be due to participant bias as only two among present study participants were diabetics.

The seroconversion rate in the present study point out that the introduction of HBV vaccination to the HCWs through infection control program in the institution was effective. But considering the prevalence of non-responders, it is recommended to perform post vaccination antibody estimation in all vaccinated HCWs to determine an initial immune response. Anti-HBs titer can be considered as an important determinant of their individual immunity to HBV infection and corresponds to the protection after any occupational exposure.

Limitation(s)

Effective scrutiny of a significant pattern of anti-HBs titer with age, sex, BMI and diabetic status was not possible with the small population. Hence, the study has to be conducted in a larger population so that associations can be determined and projected to the community. The non-responders in the study should be followed up and antibody titer should be evaluated further, as they may respond, if they were offered booster doses. But, this was beyond of the scope of present study due time restraints.

CONCLUSION(S)

Majority of the study population achieved adequate anti-HBs levels after a complete primary course of vaccination. The non-responders in the population point towards the need for post-vaccination antibody titer estimation as they may be comparatively vulnerable to HBV infection. Non-responders were advised to screen for HBV infection and be more cautious while handling infectious material, even though they are vaccinated. Routine hepatitis B immunisation for HCWs and strict post-vaccination testing with proper

documentation should be incorporated on mandatory basis under the vaccination program of every institutions. More focus should be given in creation of a relevant legislative act for the same to make dramatic reduction in the incidence of the deadly disease.

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