Original Article

Antibody to Hepatitis B Surface Antigen in Vaccinated Health Care Workers

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Abstract

Background: Health care workers (HCWs) in Armed Forces are immunised against Hepatitis B virus (HBV), however they are not subjected to anti-HBs (antibody to Hepatitis B surface antigen) assessment after primary vaccination. The present study was undertaken to determine the protection offered by HBV vaccine in HCW.
Methods: Cross-sectional study was carried out at tertiary care hospital. A total 146 HBV vaccine compliant HCW were evaluated for quantitative anti-HBs by enzyme immune assay.
Result: 129 (88.4%) subjects had protective levels of anti-HBs. Higher age at vaccination was an important risk factor in low vaccine response. Decline in anti-HBs with time was evident. Anti-HBs levels were more than 10mIU/ml in subjects even after 11 years of primary vaccination. There was no difference in protection in booster and non booster groups.
Conclusion:Age is the most important factor in HBV vaccine response. Booster dose of HBV vaccine is not necessary in healthy HCW for atleast ten years after primary vaccination. The study recommends early primary vaccination of HCW and 'initial' anti-HBs assay for confirmation of vaccine response.

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Key Words : Anti-Hepatitis B surface antigen; Health care workers; Hepatitis B virus vaccine

Introduction

Health care workers (HCW) in developing countries have the highest burden from exposure to contaminated sharps leading to infections [1]. World Health Organisation (WHO) has estimated annual global burden of 66000 cases and 261 deaths due to occupational HBV infection in HCW due to sharp injuries alone [1]. It is estimated that sharp injuries accounts for just 40-60% of occupational HBV infections in developing countries [1].

The protective efficacy of hepatitis B vaccination is directly related to the development of antibody to Hepatitis B surface antigen (anti-HBs). The efficacy of HBV vaccines has been demonstrated in clinical trials involving several groups which showed complete protection in persons who developed anti-HBs concentration of more than 10 mIU/ml following vaccination [2-4].

Male gender, smoking, obesity, human immuno-deficiency virus infection, certain HLA haplotypes, occult HBV infection and presence of a chronic disease contribute to decreased immunogenicity of the primary vaccination series [5-7]. Higher age is reported to be the most important risk factor for low efficacy of Hepatitis B vaccine in HCW [5-9]. Non-responder to HBV vaccine poses a special problem because of false sense of security after HBV vaccination. Occupational Health and Safety Administration (OHSA) recommends HBV vaccination followed by confirmation of vaccine response in all HCW by 'initial' anti-HBs assay within one to three months of primary vaccination [5,6,10].

Studies indicate that protection against serious HBV infection persists for 15-18 years despite the decline in antibody concentration [11,12]. The need for booster doses of hepatitis B vaccine after a primary vaccine series has been the subject of considerable debate. Currently, Vaccine Advisory Group in the United States and various workers do not recommend routine booster doses of hepatitis B vaccine in healthy HCW those have seroconverted after primary vaccination [6,7,10,12,13].

The present study was undertaken to determine the anti-HBs status amongst HCWs in Armed Forces and to study risk factors for non-responders.

Material and Methods

A cross-sectional study of 'HBV vaccine compliant' subjects was conducted at a tertiary care hospital. The subjects were requested to fill up a questionnaire giving their personal, health and HBV vaccine details. Blood samples were collected from each HCW and serum was stored at below - 20°C until anti-HBs test was undertaken. Commercially

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available anti-HBs EIA kit from RADIM Italia was used for quantitative assay of anti-HBs (IgG). Anti-HBs IgG standards with concentrations of 0, 10, 30, 100, 300, 1000mIU/ml, calibrated with WHO International Reference 1977 were used as controls. Manufacturer claimed sensitivity and specificity of 99.0 and 99.8% respectively. Assay was performed as per the manufacturer's instruction. All the tests were done twice and results with variation of less than 2% were averaged to get anti-HBs levels for each sample. Specimens, that gave negative, grey zone (± 20% of cut off absorbance) and unequivocal results were retested using second aliquot specimen. Further, specimens with anti-HBs concentration of 500-1000 mIU/ml, 1000-2000mIU/ml and more than 2000 mIU/ml in initial assay were diluted and retested.

HBV vaccine compliant subjects are defined as those administered minimum three doses of HBV vaccine, at a schedule of 0, 1 and 6 months; intramuscularly with dose of 20 microgram of HBsAg (Hepatitis B surface Antigen) i.e. completed minimum primary vaccination. They were further subdivided into groups as (i) Primary vaccinated < 5 years : Subjects who received primary vaccination and duration from last vaccine dose was five years or less on the date of enrolment for the study, (ii) Non-booster group or Primary vaccination > 5 years:- Primary vaccinated subjects where time gap from last vaccine dose and date of enrolment of study was more than five years and they have not taken booster dose of vaccine; (iii) Booster group-who received booster dose after five years or more of primary vaccination.

Anti-HBs positive subjects were defined as those having anti-HBs levels equal or more than 10 mIU/ml, while anti-HBs negative subjects were those having anti-HBs levels of less than 10 mIU/ml.

Chi square test was used to test the significance of difference in various groups. Z test and Student's t test were applied in finding out standard difference in mean of two groups in groups with sample size above 30 and less than 30 respectively. Pearson's product moment co-relation coefficient was used to test co-relation between age and anti-HBs concentration.

Results

A total of 254 subjects were enrolled, of which 146 (57.5%) were HBV vaccine compliant and were studied. Out of 146 subjects, 129 (88.4%) were anti-HBs positive and 17 (11.6%) HCW were negative for anti-HBs which could be due to vaccine non-response or decline in antibody levels over time post-vaccination. Anti-HBs status in relation to gender is presented in Table 1. The difference of anti-HBs status in gender was not statistically significant. Geometric mean concentration (GMC) of anti-HBs was 534.8 ± 578.7 and 708.7 ± 555.6 mIU/ml in male and female subjects respectively which was not statistically significant by Z test (z=1.73, p > 0.05, not significant).

The data of age at primary vaccination and anti-HBs status in study subjects is presented in Table 2. The inverse relation of age at primary vaccination and anti-HBs positive status was statistically significant. Mean age at primary vaccination of anti-HBs positive subject was 26.3 ± 6.7 years as against 33. ±7.6 years of anti-HBs negative group, which was significant by Z test (z=3.93, p<0.01, significant). Trend of lower anti-HBs levels with age at primary vaccination was highly significant by Pearson product moment correlation coefficient (r =-0.369, df=146, p<0.001, significant).

Anti HBs status in various vaccine groups is presented in Table 3. We did not find any statistical difference in vaccine status in booster and non-booster group (χ^2 = 0.129, df=1, p>0.10, NS, Yates correction). As expected, GMC of booster group was higher compared to non booster group due to duration from last vaccine dose; difference of GMC was statistically significant by Student's t test (t_{46}=3.074, p<0.01, Significant). Anti-HBs levels in various vaccine groups are presented in Fig. 1.

Analysis revealed 10.2% (10/98) of primary vaccinated < 5 years and 14.8% (4/27) primary vaccination > 5 years subjects were negative for anti-HBs (Table 3) and the difference was not statistically significant (χ^2 (Yates correction) = 0.107, df=1, p>0.1, NS). GMC of anti-HBs in relation to duration from last vaccine dose in primary vaccinated subjects is presented in Fig. 2. Decline in antibody concentration with time was highly significant by Pearson product moment correlation co-efficient test (r = -0.563 df =109, p<0.001, significant). Three subjects had anti-HBs concentration of more than 2000 mIU/ml and the highest anti-HBs concentration was 2845mIU/ml. Two subjects had anti-HBs concentration of more than 30 mIU/ml after eleven years of primary vaccination .

We found 15.4% smokers were anti-HBs negative as against 12.5% non-smoker; however, the difference was not statistically significant. Further, GMC of anti-HBs was lower in smoker as compared to non smoker, which was again statistically not significant by Student's t test (t_{67}=0.317, p>0.10, NS). The comparative data of smokers and non-smokers is presented in Table 4. We were unable to establish

Table 1

Gender and anti-HBs status

Status	Male	Female	Total
Vaccinated	77 (100%)	69 (100%)	146 (100%)
Anti-HBs positive	67 (87.0%)	62 (89.9%)	129 (88.4%)
Anti-HBs negative	10 (13.0%)	07 (10.1%)	17 (11.6%)

χ^2 = 0.285 df =1, p> 0.5 not significant

Table 2

Age of primary vaccination and anti-HBs status

Age	anti-HBs positive	anti-HBs negative	Total vaccinated	GMC mIU/ml
<19Yrs	14 (100%)	0	14 (100%)	644.1
20-29 years	77 (92.8%)	6 (07.2%)	83 (100%)	666.9
30-39 years	32 (84.1%)	6 (15.8%)	38 (100%)	334.1
40-49 years	6 (54.6%)	5 (45.4%)	11 (100%)	46.6
Total	129 (88.4%)	17 (11.6%)	146 (100%)	531.0

χ^2=15.66, df=2, p<0.001, highly significant

relation between anti-HBs status and overweight/obesity. Majority of the subjects had normal body mass index (BMI) (Table 5).

Discussion

The study was based on the information of HBV vaccination provided by HCW. Majority (78.9%) of them had received last HBV vaccine dose within five years. In our study 88.4% of HBV vaccine compliant subjects were anti-HBs positive. Similar immunogenicity of HBV vaccine has been reported by others [3-5]. Our study reiterated inverse relation between age at vaccination and vaccine immunogenicity. Various studies also reported higher age as the most important factor in reduced immunogenicity of HBV vaccine [6-12]. It is well documented that GMC of 'initial anti-HBs' is highest in 5-19 year age group followed by 20-49 years and lowest in 50 year and above age group [11]. This highlights the importance of HBV vaccination at the earliest for better immunogenicity and protection from occupational risk of HBV in HCW. We did not find smoking or obesity as statistically significant risk in anti-HBs negative subjects as reported by other workers [5,6], probably due to small sample size of smokers and obese subjects.

There was decline in anti-HBs levels with time after last vaccine dose. However, even after 11 years of primary vaccination, HCWs had anti-HBs levels of more than 10 mIU/ml. Various studies have shown long term persistence of anti-HBs after vaccination against HBV for 15 to 18 years [11-13]. The decline in antibody concentration was related to the initial anti-HBs concentration and age at vaccination [11]. GMC of anti-

Table 3

Anti HBs status in various vaccine compliant subgroups

Vaccine groups	anti-HBs positive	anti-HBs negative	Total vaccinated	GMC ± SD (mIU/ml)
Primary vaccinated	111 (88.8%)	14 (11.2%)	125 (100%)	536.2 ± 548.3
Primary vaccinated <5 years	88 (88.9%)	10 (10.2%)	98 (100%)	644.8 ± 610.7
Primary vaccinated >5 years (Non booster group)	23 (85.2%)	4 (14.8%)	27 (100%)	142.2 ± 174.1
Booster group	18 (85.7%)	3 (14.3%)	21 (100%)	454.7 ± 503.4

Table 4

Smoking and anti-HBs status in male

Status	anti-HBs positive	anti-HBs negative	Total vaccinated	GMC ± SD (mIU/ml)
Smoker	11 (84.6%)	2 (15.4%)	13 (100%)	417.7 ± 613.7
Non smoker	56 (87.5%)	8 (12.5%)	64 (100%)	475.1 ± 564.4
Total	67 (87.0%)	10 (13.0%)	77 (100%)	465.4 ± 569.1

χ^2 (Yates correction) = 0.028, df=1 p>0.5, not significant

Table 5

Relationship of BMI and anti-HBs status

Status	Male		Female	
	BMI <25.0	BMI >25.1	BMI <23.8	BMI >23.9
Anti-HBs positive	56 (87.5%)	11 (84.6%)	56 (91.8%)	6 (75.0%)
Anti-HBs negative	8 (12.5%)	2 (15.4%)	5 (8.2%)	2 (25.0%)
Total	64 (100%)	13 (100%)	61 (100%)	8 (100%)

χ^2 (Yates correction), 0.029, df=1, p>0.5 not significant, 0.735, df=1, p>0.5 not significant

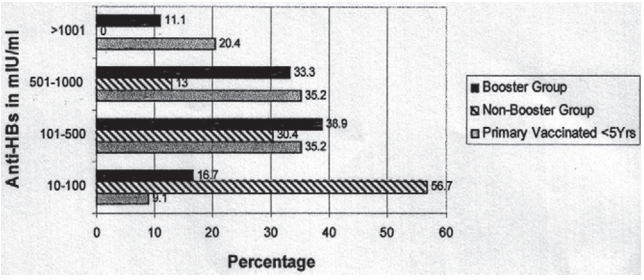

Fig. 1 : Anti-HBs in different HBV vaccine compliant groups

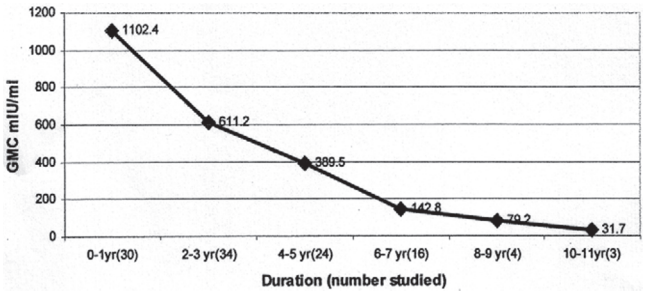

Fig. 2 : Anti-HBs in relation to duration from last HBV vaccine dose in primary vaccinated HCW

HBs of 42 and 19mIU/ml in 5-19 and 20-49 year age group subjects respectively after 15 yrs of HBV vaccination was reported earlier [11]. Thus, early age at vaccination is an important in factor in long term persistence of anti-HBs post HBV vaccination. It has been established that the disappearance of anti-HBs does not necessarily mean loss of protection, the persistence of immunological memory of peripheral blood lymphocytes serves the purpose [14]. A study from India also reported persistence of immunological memory at least 10 years after HBV vaccination [15].

US Public Health Service and various workers do not recommend booster dose in HCW after completion of primary immunisation once vaccine response has been confirmed by anti-HBs [6,7,10,12,13]. However HBV booster is recommended in immuno-compromised HCWs to maintain anti-HBs levels of more than 10 mIU/ml [6,10]. We did not find any difference in anti-HBs status in booster and non-booster group. Based on these, we do not recommend booster dose of HBV vaccine at least for ten years after primary HBV vaccination.

The standard HBV vaccine schedule of 0,1,6 month with 20 mcg HBsAg/dose as deep deltoid, intramuscular injection in HCW was found to be immunogenic as recommended by other workers [6,16]. Various studies experimenting with low dose intra-dermal route have reported decreased immunogenic response [17].

We recommend that all HCWs should undergo 'initial anti-HBs' assay within one to three months (less than six months) of last dose of primary vaccination [6,9,10]. HCW having initial anti-HBs titers of less than 10 mIU/ml should be investigated for HBV infection and if negative, they should be offer second HBV vaccination series. 30% of such individuals seroconvert after second series of HBV vaccination [6,7]. HCW not having HBV infection and not responding to second series of HBV vaccination should be diagnosed as true HBV vaccine "Non-Responder". Results of the study indicates that all HCWs should be screened for anti-HBs. If it is not feasible to screen all then HCW above 30 years of age and those with risk factors must be assessed for anti-HBs.

Conflicts of Interest

This study has been funded by research grants from the Office of Director General Armed Forces Medical Services.

Intellectual Contribution of Author

Study Concept : Surg Cdr CN Chaudhari, Col MR Bhagat
Drafting & Manuscript Revision : Surg Cdr CN Chaudhari
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