Original Article

PERSISTENCE OF IMMUNE RESPONSE AFTER HEPATITIS B VACCINATION IN MEDICAL STUDENTS AND RESIDENTS

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BACKGROUND—Among the many high risk groups, medical students and residents are especially at risk for hepatitis B virus (HBV) exposure. HBV vaccination is a well-recognized preventive strategy but there is still uncertainty about the duration of protection and revaccination need. The aim of this study was to determine the anti-HBs antibody titer using ELISA method in the years after last dose of vaccine injection.

MATERIALS AND METHODS—One hundred and fifty healthy medical students and residents who were training at Kerman University of Medical Sciences hospitals from September 2001 until September 2002, received three standard doses of recombinant HBV vaccine. For a time interval of 1, 2 – 5, and 5 – 10 years after last inoculation, the subjects were divided into three groups of 50-persons each.

RESULTS—The subjects were 85 men and 65 women with a mean age of 26.8 ± 4 years. Overall, the mean of anti-HBs antibody titer was 1,766.7 ± 227.1 IU/L with minimum end of zero and maximum level of 10,500 IU/L. Based on the time lapsed since last inoculation the mean titer of anti-HBs antibody at the end of 1 year, 2 – 5, and 5 – 10 years were 3,446.8 ± 497.4, 1,603 ± 338.6 and 250 ± 59.3 IU/L, respectively ($p < 0.001$). Protective level of antibody (> 10 IU/L) at the end of one year was seen in 98% of vaccinees. It declined to 94% in 2 – 5 year interval and to 84% in 5 – 10 years after inoculation. Most of the non-responders with antibody titer < 10 IU/L (8/12) were in the time interval 5 – 10 years.

CONCLUSION—For a revaccination schedule among medical students and residents, we suggest anti-HBs antibody detection at 5 – 10 years after primary vaccination. Revaccination should be arranged due to personal need instead of whole target population.

Keywords: ***hepatitis B vaccination; medical students; residents; immune response.***

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INTRODUCTION

Among the high risk groups, medical and health care workers are an important target population for hepatitis B virus (HBV) exposure. According to a report from University of Sydney, 71% of ward doctors, 22% of medical students, 72% of dentistry students, 50% of ward nurses, and 50% of emergency staff had received one or more needle stick injury during the previous two years.[1] In a study at a teaching hospital in Saudi Arabia the evidence of HBV markers in nonvaccinated medical staff (42.9% males, 28.6% females) was significantly greater than among medical students (25.3% males, 19.3% females) or the controls (28.6% males, 17.1 % females).[2] Prior to hepatitis B vaccine availability 10 – 30% of physicians had serologic evidence of HBV infection.[3] The annual incidence of acute hepatitis B from 1985 to 1988 in the United Kingdom was 4/100,000 in adult males and 2/100,000 in adult females, and it was estimated to be 25/100,000 for surgeons.[4]

The only preventive strategy likely to be effective in medical workers is active immunization.[5] The previous studies have shown the protective efficacy of vaccine in medical students and health care workers to be between 86 – 97%.[5 – 8] However, the persistence of such immunity and the need for booster dose injection are controversial.[6,9 – 11] In order to clarify the persistence of immune response to recombinant HBV vaccination in medical students and residents, we carried out this study.

MATERIALS AND METHODS

This cross sectional study was carried out upon 154 healthy medical students and residents who were under training in Kerman University of Medical Sciences

hospitals from September 2001 to September 2002. According to the immunization program of the Ministry of Health, they were inoculated with three doses of 20 μg hepatitis B recombinant vaccine (Heberbiovac HB, Heber Biotec SA, Cuba) at 0, 1, and 6 months intervals. Those subjects who had history of chronic disorders including previous infection with HBV, liver failure, end stage renal disease, immunosuppression and/or received corticosteroids, immunosuppressive drugs, hepatitis B immunoglobulin, less than three or more doses of HBV vaccine, were excluded from the study. In order to differentiate naturally occurring HBV infection, anti-HBc antibody (Ab) was measured. Vaccination profile and date of inoculation was recorded from local health center records or personal vaccination card for each subject.

According to time interval from last dose of vaccine injection, as (a) end of the first year, (b) 2 – 5 years, and (c) 5 – 10 years, the subjects were divided into three separate groups of 50 persons each. Anti-HBcAb and quantitative anti-HBsAb titer (IU/L) was determined by ELISA method using the Behring kits (Germany). According to anti-HBsAb level, three classes were defined: (1) nonresponders: anti-HBs level < 10 IU/L; (2) low responders anti-HBs level of 10 – 100 IU/L; and (3) good responders: anti-HBs level of > 100 IU/L.[12] The data were analyzed using Kruskall-Wallis and Student *t*-test statistical methods.

RESULTS

In this study, 154 healthy medical students and residents were evaluated by anti-HBsAb titer detection. Among them 4 (2.6%) with positive anti-HBc antibody were excluded from the study. The remaining 150 cases were 85 (56.7%) men and 65 (43.3%) women. Their age interval was 21 – 36 with a mean of 26.8 ± 4 years. Overall, the mean of anti-HBs Ab titer was 1,766.7 ± 227.1 IU/L with the lowest end of 0 and the highest level of 10,500 IU/L. According to anti-HBsAb titer, 111 (74%) persons had good response, 27 (18%) had low response and 12 (8%) had no response to HBV vaccination. Distributions of anti-HBsAb titers are shown in Table 1, according to sex and the years after vaccination. The mean titer of antibody between males and females was not significant ($p > 0.05$).

Regarding the years following last inoculation, the immune protection status in each of the three separate groups was as follows: at the end of one year, 98% had protective level of Ab as: good responders 47 (94%), low responders 2 (4%), nonresponders 1 (2%); at 2 – 5 years, 94% had protection as: good responders 39 (78%), low responders 8 (16%), nonresponders 3 (6%); and in 5 – 10 years, 84% had protection as: good responders 25 (50%), low responders 17 (34%), and non responders 8 (16%) ($p < 0.0001$) (Figure 1). Most of the low responders (17/27) and non-responders (8/12) were in the time interval 5 – 10 years after vaccination. Mean of anti-HBsAb level in the next years after the last injection was as in group (a) at the end of one year: 3,446.8 ± 497.4, in group (b) at 2 – 5 years: 1,603.1 ± 338.6, and in group (c) at 5 – 10 years interval: 250 ± 59.3 IU/L. Comparing these data, there was a significant difference in reduction of antibody titer between the first and third group ($p < 0.001$).

DISCUSSION

HBV remains a worldwide major pathogenic factor for chronic liver disease. In order to protect the health care personnel including the medical students and residents (as the future physicians), it is necessary to be certain about their immune response in vaccination era. In this study, almost all (98%) of vaccinees had protective level of antibody (>10 IU/L) at the end of one year. It declined to 94% in 2 – 5 year interval and to 84% in 5 – 10 years after inoculation. It is noticeable that most of the low-

Table 1. Anti-HBsAb titer in three separate groups of vaccinees according to sex and different time interval after vaccination.

Characteristics	Years after vaccination					
	1		2 – 5		5 – 10	
Sex (Number)	Male (22)	Female (28)	Male (24)	Female (26)	Male (39)	Female (11)
Age (year)*	23.86 ± 0.56	23.46 ± 0.88	25.21 ± 1.38	24.92 ± 0.48	32.00 ± 2.93	31.18 ± 1.72
Ab titer (IU/L)**	2448.4 ± 689.8	4231.3 ± 977.7	1228.4 ± 300.3	2009.1 ± 623.6	215.4 ± 55.5	372.9 ± 187.1
p value***	$p > 0.05$		$p > 0.05$		$p > 0.05$	

*Values are shown as mean ± standard deviation; **Values are shown as mean ± standard error of the mean; ***Student *t*-test.

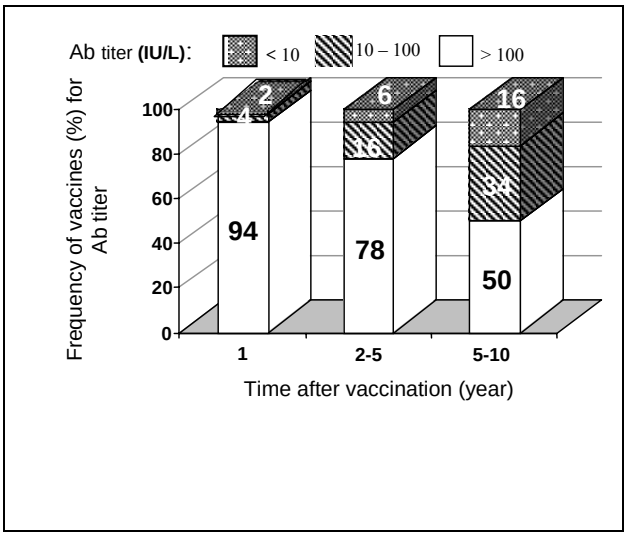


Figure 1. Immune status of three separated groups of HBV vaccines during different time intervals after original vaccination.

responders and nonresponders were in the 5 – 10 year period after the last inoculation. Serologic evidence of prior HBV exposure was present in 2.6% of these subjects while it is estimated that over 35% of Iranian population have been exposed to HBV.[13] This denotes the necessity of immune protection for such a highly unexposed group who are continuously in touch with HBV. As in our study, no influence of sex was seen in antibody response in Panizo Delgado and Simo Minana studies.[8,10]

There is still uncertainty about the persistence of the vaccine induced protection and the need for revaccination among different authors. One opinion is that the vaccine length of protection is related to the maximum level of anti-HBs response. The maximum anti-HBs titers is reached between 1 and 2 months after the last vaccine dose, then it begins to decrease rapidly during 20 – 24 months, but subsequently the fall is slower.[10] According to Coursaget's recommendation on a formal statistical model,[9] in order to maintain anti-HBs titers above 10 IU/L for at least 90% of vaccinees, subjects should be revaccinated after 2.5, 10 or 40 years, depending on whether titer at booster is around 10,100 or 1,000 IU/L, respectively. In a Russian study[14] recombinant Engerix B vaccine response was tested on medical students, health care workers, and patients of hemoperfusion centers. The protective level of antibody decreased from 93.9%, 91.4%, and 76.1 in the first month post vaccination to 82.5%, 77.2%, and 53.3% after a year, respectively. In Dienstag study on 658 health care personnel, levels of anti-HBsAb increased gradually during the months after plasmatic HBV vaccination. It was positive in 96.6% of vaccine recipients at 12 months and in 98.9% at 18 months, when the study ended.[5] Chadha[11] studied the long-term persistence of anti-HBsAb in 34 health care workers following three dose injections. In that study, group A (n = 16) received booster vaccine after 3 years whereas group B (n = 18) did not. After 10 years of follow-up, 6/15 (40%) of group A and 3/16 (~19%) of group B had protective anti-HBsAb. They concluded that persistence of immunological memory remains for at least 10 years. The result of serconversion rate after plasmatic HBV vaccination for 310 health professionals in a general hospital in Spain was 95%.[8] Simo Minana et al[10] studied HBV vaccine immunoresponsiveness in 427 healthy preadolescents after three-dose scheduled vaccination with recombinant Engerix B vaccine. Anti-HBsAb was detected one month after the last vaccine injection. They found 100% protective antibody in vaccinees and concluded that the central 50% of the sample would be protected during a period between 7.5 – 10.5 years. So, they advocate for a single booster dose 10 years after primary vaccination. In another study Ayerbe[15] showed a protective level of anti-HBsAb 6.5 years after vaccination in 462 healthy subjects and did not recommend booster dose injection until this time in immunocompetent population. In Amini et al[16] report, the seroconversion rate (anti-HBsAb > 10 IU/L) one month after three-dose scheduled HBV vaccination (Heberbiovac, Cuba) for children and adults were 100% and 93.7%, respectively. In this study seroconversion rate in adults decreased to 91.1% after one year and reached 81.8% after two years. In another study in Iran, Shokrgozar[17] showed a protective level of antibody in 95.2% of healthy adult individuals vaccinated with recombinant Heberbiovac HB vaccine.

In most of these studies, subjects were followed-up for 1 – 2 years post-HBV vaccination[5,8,10,13,16,17] and some, for up to 10 years.[11,15] Because of some limitations in follow-up of longer periods, we carried out this study in a cross sectional form and on a larger group with resembling characteristic and demographic features but with differing vaccination time. We believe that the comparison of antibody titer in these three groups with different vaccination time interval can replace the long-term follow-up of one single group over time. According to the results of the present study, there was a reduction in Ab titer during years after vaccination, but 84% of vaccinees had protective level of Ab in their sera even for more than 5 years. The mean of Ab titer after 5 years was 250 ± 59.3 IU/L, which means maintenance of immunological memory for at least

5 – 10 years. The results obtained in this study are in agreement with the results of other studies done in Iran[16,17] and also in other countries.[5,8,10,14] Our results showed that HBV vaccination with Heberbiovac HB (Cuba) vaccine is successful in inducing immune response nearly as other plasma derived or recombinant vaccines.

In conclusion, according to the above mentioned results, for a high risk group population such as medical students and residents, who are at continuous exposure to HBV, it is reasonable to determine the anti-HBsAb response at one month post boosting. However, in order to confirm the persistence of immune protection, we strongly suggest detection of the anti-HBsAb titer at 5 – 10 years after the last inoculation. So, the revaccination schedule could be arranged on the basis of personal need without the cost of revaccination for the whole target population.

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REFERENCES

1. de Vries B, Cossart YE. Needlestick injury in medical students. *Med J Aust*. 1994; 160: 398 – 400.

2. al-Sohaibani MO, al-Sheikh EH, al-Ballal SJ, Mirghani MA, Ramia S. Occupational risk of hepatitis B and C infections in Saudi medical staff. *J Hosp Infect*. 1995; 31: 143 – 7.

3. Diekema DJ, Ferguson KJ, Doebbeling BN. Motivation for hepatitis B vaccine acceptance among medical and physician assistant students. *J Gen Intern Med*. 1995; 10: 1 – 6.

4. Llewellyn LJ, Harvey I. Hepatitis B vaccination: how many doctors are fully covered ? *J Public Health Med*. 1994; 16: 352 – 6.

5. Dienstag JL , Werner BG , Polk F , Snydman DR, Craven DE, Platt R, et al. Hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. *Ann Intern Med*. 1984; 101: 34 – 40.

6. Peces R, Laures AS. Persistence of immunologic memory in long-term hemodialysis patients and healthcare workers given hepatitis B vaccine: role of a booster dose on antibody response. *Nephron*. 2001; 89: 172 – 6.

7. Marinho RT, Pedro M, Ramalho F, Velosa J , De Moura MC. Vaccine against hepatitis B. Eight years of experience [in Portuguese]. *Acta Med Port*. 1998; 11: 971 – 7.

8. Panizo Delgado A, Martinez Artola V. Hepatitis B vaccination: immunogenicity of the plasmatic vaccine in hospital personnel [in Spanish]. *Med Clin (Barc)*. 1989; 92: 401 – 4.

9. Coursaget P, Yvonnet B, Gilks WR, Wang CC, Day NE, Chiron JP. Scheduling of revaccination against hepatitis B virus. *Lancet*. 1991; 337: 1180 – 3.

10. Simo Minana J, Gaztambide Ganuza M, Fernandez Millan P, Pena Fernandez M. Hepatitis B vaccine immunoresponsiveness in adolescents: a revaccination proposal after primary vaccination. *Vaccine*. 1996; 14: 103 – 6.

11. Chadha MS, Arankalle VA. Ten year serological follow up of hepatitis B vaccine recipients. *Indian J Gastroenterol*. 2000; 19: 168 – 71.

12. Sherlock S, Dooley J. Hepatitis B virus and hepatitis delta virus. In: Sherlock S, Dooley J, eds. *Diseases of the Liver and Biliary System*. 11th ed. Oxford: Blackwell Science; 2002: 285 – 300.

13. Merat S, Malekzadeh R, Rezvan H, Khatibian M. Hepatitis B in Iran. *Arch Iranian Med*. 2000; 3: 192 – 201.

14. Shakhgil`dian IV, Khukhlovich PA, Saving EA, Kuzin SN, Anan'ev VA, Sergeeva NA, et al. Risk of infection with hepatitis B and C viruses of medical workers, patients in the hemodialysis ward, and vaccine prophylaxis of hepatitis B infection in these populations [in Russian]. *Vopr Virusol*. 1994; 39: 226 – 9.

15. Ayerbe MC, Perez Rivilla A, ICOVAHB Group. Assesment of long-term efficacy of hepatitis B vaccine. *Eur J Epidemiol*. 2001; 17: 150 – 6.

16. Amini S, Andalibi S, Mahmoodi M. Anti-HBs response and its protective effect in children and adults receiving hepatitis B recombinant vaccine in Tehran. *Iranian J Med Sci*. 2002; 27: 101 – 5.

17. Shokrgozar MA, Shokri F. HLA-associated antibody response to recombinant hepatitis B vaccine in healthy Iranian adults. *Iranian J Med Sci*. 1999; 24: 98 – 103.

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